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COLUMBIA RIVER BASIN FISH CONTAMINANT SURVEY

VOLUME I

Appendix C

Toxicity Profiles

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CRITFC TOXICOLOGICAL PROFILES

OVERVIEW:

Using toxicology data to develop risk factors for non-cancer and cancer:

The EPA has developed factors which describe the chronic toxicity of chemicals in a quantitative manner. The methodology to develop quantitative toxicity factors is a systemic approach to organizing scientific information in a consistent, transparent fashion. There are different methods for cancer endpoints and for non-cancer endpoints. Mathematically combining the toxicity factors with concentrations of chemicals which contact the human body (by ingestion or other exposure routes) provides a tool for ranking chemical concentrations and focusing efforts on exposures where additional public health investigations, remedial measures or other actions may be warranted. Chronic toxicity is that which occurs following consistent, long term exposures. The EPA generally defines these long term exposures to be greater than 10% of a lifespan, or approximately 7 years.

The methodology for developing a chemical-specific quantitative toxicity factor for non-cancer effects, known as a Reference Dose (RfD), begins by reviewing all the known adverse non-cancer health effects associated with human or animal exposures to the chemical. The adverse health effect which occurs at the lowest exposure is identified, and that information is carried forward through the RfD methodology. When the data are sufficient, the exposure associated with no observed adverse health effects (called the NOAEL, the no-observed-adverse-effect-level) is the numeric value used to develop the RfD. Although separate RfDs could be developed for each possible adverse health effect caused by a chemical, for the purposes described above (for focusing and deciding about additional efforts) the effect at the lowest exposure is used. Decision rules in the RfD methodology direct the choice of uncertainty factors which are applied to the exposure estimate (the NOAEL or, when a NOAEL is not available, the lowest known exposure). Uncertainty factors can range from a value of 3 to 10,000 with the lowest values indicating strong human evidence and a high degree of confidence in the information. The resulting RfD is an estimated daily human exposure, including sensitive populations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Even when an RfD has a low uncertainty factor value (indicating high confidence), difficulties in estimating true long term exposures mean that predicting any individual person's health outcome is not possible by this method. However as stated previously, this approach is useful focusing and deciding about additional efforts.

The methodology for developing a chemical-specific cancer factor, known as a Cancer Slope

Factor or Cancer Potency Factor, begins in a similar fashion by assembling all reports of cancer effects associated with human or animal exposures to the chemical. The scientific data is first

summarized with respect to the likelihood that exposure could result in human cancer. Only in the case where evidence clearly indicates human exposures resulting in confirmed cancer is a chemical given a weight-of-evidence classification of "A", known human carcinogen. In all other cases, a lesser classification is given ranging from "B1" to "D". The "B1" weight-of-evidence classification indicates that experimental animal evidence is strong but that human evidence is limited. The "B2" weight-of-evidence classification indicates sufficient animal evidence but no human evidence is available. While the "C" weight-of-evidence classification indicates that only limited animal evidence is available. And, "D" indicates that there is not enough scientific data for a classification. In the future, the "A" through "D" classifications will be discontinued and only verbal descriptors will be used.

Once classified, the data which provides the greatest scientific rigor is chosen for mathematical modeling. Modeling is necessary because information is needed for the purposes described above (for focusing and deciding about additional efforts). In contrast, the available data are for exposures which are much higher than those expected from contact with environmental media. Additionally, present day scientific methods are not sensitive enough to measure effects which occur at environmental exposure levels. Hence, a model is used to extrapolate results from higher to lower exposures. When no other data is available, the model assumes that the cancer response which occurs at higher exposures is the same at lower exposures.

The resulting Cancer Slope Factor or Cancer Potency Factor is a probability estimate for the occurrence of cancer without regard to severity or significance of the cancer. Stated in another way, it is a probability of the occurrence (or incidence) of any type of cancer and not the probability of death due to cancer. It is a numeric statement of risk associated with a consistent, long term (chronic) exposure dose. The higher the value of the Cancer Slope Factor or Cancer Potency Factor, the higher the likelihood that cancer may be associated with the estimated chronic exposure dose. Due to the use of extrapolation and the uncertainties with estimating true long term exposures, even when a chemical has an "A" weight-of-evidence classification predicting any individual person's cancer outcome is not possible by this method. However as stated previously, this approach is useful for focusing and deciding about additional efforts.

TOXICOLOGICAL PROFILES

PESTICIDES:

Aldrin: (1R,4S,4aS,5S,8R,8aR)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro1, 4:5,8-dimethanonaphthalene; CASRN 309-00-2 (See also Dieldrin)

Aldrin belongs to the "cyclodiene" series of chlorinated pesticides, which also includes the related compounds Dieldrin, Endrin, Chlordane, Heptachlor, and Heptachlor epoxide. Aldrin's chemical nomenclature is also sometimes abbreviated as HHDN. As a pesticide residue, Aldrin, per se, is rarely detected in its original chemical form. This is because in the environment, and when sequestered in biota, Aldrin quickly undergoes epoxidation, to form the (very stable and persistent, and very similar in toxicity) compound, Dieldrin. Therefore, much of the Dieldrin detected in the global environment today may have originally been applied to the environment as either Dieldrin *per se*, or as Aldrin.

From the 1950's until the early1960's, both Aldrin and Dieldrin were applied extensively as pesticides in the United States, especially on crops such as corn and cotton. They were also used extensively in the extermination of termites in soil, until these uses were banned by EPA in 1974. At the present time, all uses of both Aldrin and Dieldrin in the USA have been canceled. Because of the persistence and slow degradation of aldrin/dieldrin, small quantities of dieldrin are still occasionally detected at low levels in various environmental samples.

Like other organochlorine insecticides, the primary target of acute poisoning from aldrin and

dieldrin is the nervous system. Severe acute exposures to these cyclodiene insecticides can result in sudden onset of convulsions, as well as other manifestations like headache, dizziness, nausea, vomiting, in coordination, tremor and mental confusion. A second specific target organ for aldrin/dieldrin–especially at lower doses over time–is the liver. In animal studies, aldrin/dieldrin have also been shown to be developmental toxicants. The Oral Reference Dose (RfD) for Aldrin is 3E-5 mg/kg/day, based on a critical effect of liver toxicity observed in an oral rat feeding study. The rat Lowest Observable Adverse Effect Level (LOAEL) was 0.025 mg/kg/day. No NOAEL was established from this study. Uncertainty factor is 1000, because of the lack of a NOAEL, and to allow for animal to human extrapolation, and for variability within human populations. Confidence in the RfD is medium.

Aldrin and Dieldrin are both classified by EPA as Group B2 (possible human) carcinogens. This is based on observations of significant tumor response after oral dosing studies in three strains of mice. In addition, five related chemicals–dieldrin, chlordane, heptachlor, heptachlor epoxide and chlorendic acid have also induced malignant tumors in similar mouse bioassay studies.

The oral carcinogenicity slope factor for Aldrin is 1.7E+1 mg/kg/day; essentially identical to the slope factor value–1.6E+1 mg/kg/day which has been calculated independently for Dieldrin.

Dieldrin: (1R,4S,4aS,5R,6R,7S,8S,8aR)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8, 8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene; CASRN 60-57-1

Dieldrin is structurally related to various other pesticide compounds ("cyclodienes") which are known to produce tumors in rodents. These related compounds include aldrin, endrin, chlordane, heptachlor, and heptachlor epoxide. Dieldrin's chemical nomenclature is sometimes abbreviated as HEOD. Dieldrin is no longer used as a pesticide in the United States. However, its relative persistence and lipophilicity enables it to still occur as a contaminant in various environmental media, as a result of past use. Dieldrin in the environment is also a result of the past use of its close relative, Aldrin, which is converted via natural processes into the more stable and persistent dieldrin.

Organochlorine pesticides like aldrin and dieldrin are neurotoxicants, for which acute signs of toxicity can include: hyperexcitability, seizures, convulsions and dizziness. Chronic signs of toxicity include: intermittent muscle twitching, psychological disorders, loss of consciousness and convulsions.

The oral RfD, 5E-5 mg/kg/day, is based on a two-year rat study which observed liver abnormalities (increased liver weight and liver /body weight ratio). NOAEL from the rat data was 0.005 mg/kg/day. LOAEL was 0.05 mg, kg/day. An uncertainty factor of 100 is used to account for interspecies variability (subfactor of 10) and for sensitive subpopulations (subfactor of 10). Confidence in the RfD is medium because the study is older, has relatively little detailed data, and lacks reproductive studies.

The weight of evidence for carcinogenicity for dieldrin is classified as B2 (probable human carcinogen), and is based upon carcinogenic effects in various strains of mice when administered orally. However, several similar studies with various strains of rats of both sexes did not product positive results for carcinogenicity, thus making the available rodent data somewhat equivocal.

The oral carcinogenicity slope factor for Dieldrin is 1.6E+1 mg/kg/day.

Chlordane: 1,2,4,5,6,7,8,8-Octachloro-2,2,2a,4,7,7a-hexahydro-4,7-methano-1H-indene; CASRN 12789-03-6 (for technical chlordane)

Technical Chlordane is not a single chemical, but is a mixture of several closely related chemicals, which consist of some of the various chlordane isomers and metabolites listed below.

alpha-Chlordane: (*cis*-Chlordane)	CASRN 5103-71-9
gamma-Chlordane: (*trans*-Chlordane)	CASRN 5103-74-2
oxy-Chlordane:	CASRN 27304-13-8
alpha-Chlordene:	CASRN 56534-02-2
gamma-Chlordene:	CASRN 56631-38-4
cis-nonachlor:	CASRN 5103-73-1
trans-nonachlor:	CASRN 39765-80-5

Chlordane belongs to the cyclodiene group of pesticides, and is structurally quite similar to Heptachlor, and Heptachlor Epoxide. In many instances, Heptachlor is also a minor component of technical Chlordane. Other cyclodiene pesticides in this general chemical group include Aldrin, Dieldrin, Endrin, and Endosulfans I and II.

Chlordane does not occur naturally in the environment. It was commonly used as a pesticide in the USA from the late 1940's until the late 1980's. Until 1983, it was used on corn and citrus, and also lawns and gardens. Prior to EPA's banning of all uses of chlordane in 1988, it was also used for structural pest control, especially around slab housing foundations in warm climates. Like most of the other cyclodiene pesticides, chlordane degrades very slowly. Various of its metabolites can stay in soil for over 20 years, and can bioaccumulate in the tissues of higher organisms.

Exposure to chlordane occurs mostly from eating contaminated foods, such as root crops, meats, fish, and shellfish, or from touching contaminated soil. In people and animals, acute exposure to chlordane affects primarily the nervous system, the digestive system, and the liver. Sufficiently large oral doses can cause convulsions and death. The oral RfD for chlordane is 5E-4 mg/kg/day. This is based on a 104 week mouse feeding study, from which a NOAEL of 0.15 mg/kg/day was established. LOAEL from this study was 0.75 mg/kg/day. The critical effect toxic endpoint at low dose was hepatic necrosis. IRIS lists an overall uncertainty factor of 300 for this RfD. Confidence in the RfD is medium.

For carcinogenicity, IRIS lists Chlordane in Group B2 (probable human carcinogen). This designation is based on findings of hepatocellular carcinoma in mice, and hepatocellular adenomas in rats which had been orally dosed during various chronic laboratory studies.

The oral carcinogenic slope factor for Chlordane is 3.5E-1 mg/kg/day.

With respect to the specific individual components of the typical chlordane mixture (see above listings for names and CAS Nos.), relatively little toxicological information is available. No

RfDs or slope factors have been developed for these various chlordane isomers and metabolites. Because of structure-activity relationships, it is likely that their toxicities and critical target effects are somewhat similar in the general sense, to those of chlordane *per se.*

For Alpha-Chlordene-apparently one of the least acutely toxic members of this cyclodiene group-the Registry for Toxic Effects of Chemical Substances (RTECS) lists a rat acute oral LD50 of 10,200 mg/kg. This makes it about one twentieth as acutely toxic as Chlordane (Acute LD50: 367 - 515 mg/kg), at least to the rat.

Chlorpyrifos: chlorpyrifos-ethyl; O,O-diethyl,O-(3,5,6-trichloro-2-pridinyl)phosphorothioate; CASRN 2921-88-2

Chlorpyrifos is a widely-used organophosphate pesticide. It is also known as "chlorpyrifos ethyl". Chlorpyrifos was first marketed in 1965, and came into greatly increased use after 1988, when restrictions and bans were imposed on the pesticide chlordane for termite applications. Chlorpyrifos is rather atypical among the organophosphate pesticide group, because it also possesses a high degree of chlorination. This chlorination imparts certain properties not typically noted for this general class of compounds; making chlorpyrifos somewhat more difficult to degrade in the environment, and more lipid soluble. Chlorpyrifos is thus poorly water soluble, adsorbing readily to soil and sediment, and more persistent than most other pesticides in this general group.

Although few epidemiology studies on this pesticide have been undertaken, the EPA has recently concluded that chlorpyrifos is one of the leading causes of insecticide poisoning in the United States. Data from 1993-94 indicate that some 4000 - 5000 cases of accidental chlorpyrifos exposure were reported. As with all reports of pesticide exposure and poisoning symptoms, this estimate probably underestimates the true extent of the problem. It is estimated that chlorpyrifos is applied to homes and lawns about 20 million times annually. The widespread use of this pesticide in households to control fleas, termites and other pests, as well as many uses on agricultural crops has also resulted its increasingly frequent detection as a residue at low concentrations in recent years. In a 1993 environmental review of the environmental fate of chlorpyrifos, bioconcentration factors (BCF) were reported in a variety of fish under both field and experimental conditions. The upper range of these BCF were as high as 5100, which suggests that bioconcentration of chlorpyrifos is moderate to very high.

Because of reports of toxicity and other problems related to its somewhat greater persistence, the manufacturer of chlorpyrifos voluntarily withdrew most of the indoor and pet uses of this chemical in 1997. In July, 2000, EPA also reached an agreement with chlorpyrifos registrants to eliminate and phase out certain food uses, which pose the greatest risks to children. The agreement also cancels and phases out nearly all indoor and outdoor residential uses, and reduces risks to workers. Essential and more low-risk uses of chlorpyrifos such as in containerized baits, non-structural wood treatments, fire ant control and so forth will be allowed to continue.

Like other members of the organophosphate group, the key mechanism of toxic action for

chlorpyrifos is inhibition of the enzyme acetylcholinesterase (also called cholinesterase or ChE),

which is essential to the proper functioning of the nervous system. It readily inhibits plasma ChE at low doses, and red blood cell ChE at higher doses. At sufficiently high acute doses, inhibiting cholinesterase enzyme with organophosphate pesticides like chlorpyrifos causes various parasympathomimetic neurologic symptoms like salivation, lacrimation, dizziness, changes in heart rate, nausea, diarrhea, visual problems, muscle weakness or tremors, confusion, etc. There is also recent preliminary information from NIOSH suggesting that exposure to chlorpyrifos might also result in delayed neurological effects, particularly among subjects with a prior history of poisoning.

The widespread and extensive use of this pesticide makes it relatively prevalent at trace levels in many environmental exposure pathways. In the body, chlorpyrifos is metabolized in the liver to form the major metabolic product, 3,5,6-trichloro-2-pyridinol (TCP). TCP is also a major metabolite of the closely related insecticide, chlorpyrifos-methyl, as well as of the herbicide triclopyr (Garlon). TCP is excreted in the urine, and can typically be found in urine for several days post-exposure to chlorpyrifos. When detected in urine samples by properly equipped analytical laboratories, TCP is a significant biomarker indicative of possible recent chlorpyrifos exposure. It is estimated by NIOSH that approximately 82 per cent of U.S. adults have detectable urinary levels of TCP, with a mean level of about 4.5 micrograms per liter in the general U.S. population.

The oral RfD for chlorpyrifos is 3E-3 mg/kg/day, based on a 1972 human cholinesterase inhibition study. The NOAEL for this study was 0.03 mg/kg/day, with a LEL of 0.1 mg/kg/day. This RfD has an uncertainty factor of 10, which is the standard factor which is utilized to allow for the range of human sensitivity for cholinesterase (ChE) inhibition. IRIS indicates that confidence in the database is medium. Although several doses were used, only 4 males per dose were studied. However, the experimental data for rats, rabbits, mice, and dogs reveal NOAEL data similar for that noted for humans.

Chlorpyrifos has not undergone a complete evaluation under EPA's IRIS program for evidence of carcinogenic potential. However, like most other organophosphate pesticides, it is not anticipated to have significant carcinogenic activity.

Chlorpyrifos Methyl: O-O-Dimethyl-O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate;

The mechanism of action of chlorpyrifos methyl-cholinesterase inhibition-is essentially identical to that of chlorpyrifos ethyl (chlorpyrifos). Likewise, the environmental behavior and other properties are similar to chlorpyrifos ethyl (see profile for chlorpyrifos).

DDT SERIES

DDT: 1,1,1-trichloro-2,2-*bis*(p-chlorophenyl)ethane; CASRN 50-29-3
DDE: 1,1-dichloro-2,2-*bis*(p-chlorophenyl)ethylene; CASRN 72-55-9
DDD: 1,1,-Dichloro-2,2-*bis* (p-chlorophenyl) ethane; CASRN 72-54-8
DDMU: 1,1-bi s(p-chlorophenyl)-2-chloro-ethylene; CASRN 1022-22-6

DDT, and its structural analogs DDE and DDD, are organochlorine pesticide residues. DDT products are sometimes contaminated with DDE and DDD. DDMU is a breakdown product of the DDT series, and is occasionally detected in environmental media.

DDT and its analogs do not occur naturally in the environment. The DDT group was once used very extensively to control insects on agricultural crops, as well as to control insects which carry diseases like malaria and typhus. In 1972, the EPA banned all uses of DDT in the united states, except for public health emergencies. However, DDT is still utilized in under-developed countries, especially to control malaria.

When DDT is applied to the environment, much of it is gradually changed over time into DDE, which is normally the most prevalent DDT residue found in various environmental media today. DDD is also a breakdown product of DDT. The DDT group lasts a very long time in soil; half the DDT in soil will break down in about 2-15 years, depending on local conditions.

Organochlorine pesticides are neurotoxicants for which acute signs of toxicity include parasthesia, ataxia and dizziness. At high levels, these chemicals can damage the nervous system, causing excitability, tremors, and seizures. Chronic signs of toxicity include anorexia, mild anemia, tremors, seizures, muscular weakness, hyperexcitability and nervous tension. Immunological effects and developmental toxicity have also been associated with DDT. Exposure to DDT, DDE and DDD occurs mostly from eating contaminated foods, such as root and leafy vegetables, meat, fish, and poultry.

The oral RfD for DDT is 5E-4 mg/kg/day, and is based on a chronic rat feeding study (utilizing a mixture of 81 percent p,p' DDT isomer and 19 per cent o,p' DDT isomer). Critical effect was hepatocellular hypertrophy (liver lesions) in the exposed population. The NOAEL was 0.5 mg/kg/day, based on a daily dose of 1 part per million in the diet. The LOAEL for DDT was calculated at fivefold this dosage (0.25 mg/kg/day). Male rats were more sensitive to the low-

dose effects of DDT than were female rats. An uncertainty factor of 100 is used to account for interspecies conversion (sub-factor of 10) and to protect sensitive human subpopulations (sub-factor of 10). Confidence in the RfD is medium to low, because the study was of shorter duration, and lacked a clear NOAEL for reproductive effects. IRIS does not list specific RfD's for DDE or DDD. However, because their structures and toxicities so closely resemble that of DDT, for purposes of this study we will assume that they (and their various ortho-and para-isomers) also have the same RfD as DDT.

The cancer weight of evidence for DDT, DDE, and DDD is classified as "B2" (probable human carcinogen). The carcinogenic slope factor for both DDT and DDE is 3.4E-1mg/kg/day. For DDT, this is based on the observation of tumors (usually liver) in various laboratory studies of orally-dosed mice and rats. For DDE, the slope factor is based on the incidence of liver tumors including carcinomas in two strains of mice, and in hamsters, as well as thyroid tumors in dietary-dosed female rats. DDD, which is considered less toxic than DDT, has a cancer slope factor of 2.4E-1 mg/kg/day, based on an increased incidence of lung tumors in male mice, liver tumors in female mice, and thyroid tumors in male rats.

Limited toxicity information is available for DDMU. According to RTECS database, the mouse oral LD50 for DDMU is 2700 mg. kg, with tremor and behavioral changes being the most noteworthy signs of acute toxicity. At this time, no oral RfD, carcinogenicity evaluation, or oral carcinogenic slope factor are available for DDMU.

For purposes of this report, cancer and non-cancer risks from the DDT series will be respectively expressed as the sums of the individual risks of the para-para and ortho-para isomers of DDT, DDE, and DDD.

Methoxychlor: 2, 2-bis(p-methoxyphenyl)-1,1,1-trichloroethane; methoxy DDT; CASRN 72-43-5

Methoxychlor is essentially a less-toxic form of the organochlorine pesticide, DDT, in which a methoxy group replaces the (more persistent and biologically active) chlorine molecule on one of the phenyl groups of the basic DDT molecule (see toxicology profiles for DDT series).

Methoxychlor is also considered to have estrogenic activity, both *in vivo* and *in vitro*. Recent evidence published in the literature at large indicates that both methoxychlor and its metabolites

have estrogen-like activity, with several metabolites having proestrogen activity.

The oral RfD for methoxychlor is 5E-3 mg/kg/day, based on a 1986 rabbit teratology study in which the critical toxicologic endpoint was excessive litter loss. NOAEL from this study was 5.01 mg/kg/day, with a Lowest Effect Level (LEL) of 35.5 mg/kg/day. IRIS shows uncertainty factor of 1000 applied to this RfD, to account for the inter-and intra-species differences. An additional factor of 10 was used to account for the poor quality of the critical study and for the incompleteness of the data base on chronic toxicity. Confidence in the data, and the RfD, is low.

In terms of likelihood for possible carcinogenicity, EPA/IRIS has classified methoxychlor in Group D (not classified as to human carcinogenicity). This is due to the unavailability of human data, and the inconclusive nature of existing evidence from animal studies regarding carcinogenicity of this substance. Methoxychlor has been assayed for carcinogenicity in numerous chronic dietary, dermal, and injection studies in rats and mice, as well as a limited oral study in dogs. Regulatory bodies including the National Cancer Institute (NCI, 1978), International Agency for Research on Cancer (IARC, 1979), and the EPA (EPA, 1987) have all concluded that the experimental evidence in animals does not support the contention that methoxychlor is a carcinogen.

Dichlorobenzophenone (Dicofol pesticide metabolite): CASRN 90-98-2

4,4'-Dichlorobenzophenone is a major breakdown product of the organochlorine pesticide, Dicofol (2,2,2-trichloro-1,1-bis(4-chlorophenyl)ethanol; also known under the trade name of "Kelthane"), CASRN 115-32-2. Alkaline hydrolysis of dicofol in the environment produces dichlorobenzophenone and chloroform. Under anaerobic incubation, dicofol has a half life of less than 30 days, degrading to 4,4'-dichlorobenzhydrol and 1,1'(p-chlorohenyl)-2,2-dichloroethanol.

Dicofol is structurally very similar to DDT and Methoxychlor (see toxicological profiles for these related compounds), and was initially registered in 1957 as a foliar spray on agricultural crops and ornamentals, and in or around agricultural and domestic buildings for mite control. It was at one time heavily used to control mites on cotton and citrus crops.

In the ensuing years after its introduction, dicofol products were subsequently found to contain a number of DDT analogs as manufacturing contaminants. These impurities included the o,p' and

p,p' isomers of DDT, DDE, DDD, and a substance called "extra -chlorine DDT", or tetrachloro-DDT. In May, 1986, EPA required that these DDT contaminants be reduced to less than 2.5 per cent, in the technical grade dicofol compound. Because the major manufacturer was technically unable to meet these requirements, EPA ordered an immediate halt in September, 1986 to the distribution and sale of dicofol pesticide active ingredients, and cancelled product registrations which contained dicolfol as an active ingredient. A significant component underlying this decision was based on the need to protect perigrine falcons and other raptor populations--, as well as aquatic organisms--from DDT-mediated reproductive failure.

Endosulfan: 6,7,8,9,10,10-hexachloro-1,5,5a,6,9,9a-hexahydro-6,9- methano-2, 4,3-benzodioxathiepin-3-oxide; CASRN 115-29-7 (for both isomers together)

Endosulfan I: (Alpha isomer): CASRN 959-98-8

Endosulfan II: (Beta isomer): CASRN 33213-65-9

Endosulfan–also known as Thiodan-- is a manufactured insecticide, and does not occur naturally. It is used to control various insects on food crops like grains, tea, fruits and vegetables, as well as on nonfood crops like cotton and tobacco. It is also used as a wood preservative. It has not been produced in the USA since 1982; however it is still used here to produce other chemicals.

Organochlorine pesticides like endosulfan and related compounds are neurotoxicants, for which acute signs of toxicity include: hyperexcitability, seizures, convulsions and dizziness. Chronic signs include: intermittent muscle twitching, psychological disorders, loss of consciousness and convulsions. Neurological effects have been demonstrated at high doses. In animal studies, long-term exposure to low levels of endosulfan have been shown to affect the kidney (glomerulonephritis), testes, and liver. Effects on the immune system, and decreased weight gain were also noted. Developmental toxicity (rat) has also been associated with endosulfan in laboratory feeding studies.. Exposure to endosulfan occurs mainly from eating contaminated food.

Endosulfan, as the usual mixture consisting of alpha and beta isomers, has an oral RfD of 6E-3 mg/kg/day, based on laboratory oral feeding studies in two animal species. One set of data was generated from a 1989 2-year rat feeding study. The endosulfan rat NOAELs were 0.6 mg/kg/day (male), and 0.7 mg/kg/day (male). LOAEL for male rats was 2.9 mg/kg/day, while

the female rat LOAEL was 3.8 mg/kg/day. Critical toxicologic endpoints were reduced body weight gain in both sexes, and increased incidence of marked progressive glomerulonephritis (kidney damage) and blood vessel aneurysms in males. Other data supporting this RfD come from a 1989 one-year dog feeding study, in which decreased weight gain was noted in males, and neurologic findings were seen in both sexes. NOAEL for the dog feeding study was 0.57 mg/kg/day, with a LOAEL of 1.9 mg/kg/day (females) and 2.1 mg/kg/day (males). An uncertainty factor of 100 is used to account for intraspecies variability (subfactor of 10) and interspecies extrapolations (subfactor of 10). Confidence in the RfD is medium, due to the lack of developmental data in a second species.

Note: for this report, this oral endosulfan RfD (6E-3 mg/kg/day) will also be assumed to be applicable for both alpha and beta isomers because of their similar toxicities.

At this time endosulfan and its isomers have not been fully evaluated and classified by EPA/IRIS for evidence of carcinogenicity.

Endosulfan Sulfate: CASRN 1031-07-8

This compound is an endosulfan reaction product (from either oxidation, biotransformation or photolysis). According to the ATSDR Toxicological Profile for endosulfan, there is very little difference in toxicity between these two products.

At this time, there is no oral RfD listed for endosulfan sulfate, on IRIS or HEAST.

Note: for purposes of this report, the oral RfD for endosulfan sulfate will be assumed to be identical for that set forth in IRIS for endosulfan (6E-3 mg/kg/day).

At this time, endosulfan sulfate has not been fully evaluated and characterized by EPA /IRIS for evidence of carcinogenicity.

Endrin: 1,2, 3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-endo-1,4:5,8-dimethanonaphthalene; CASRN 72-20-8

Endrin, like aldrin and dieldrin, is also a cyclodiene pesticide, and is the most acutely toxic

pesticide of this group. It was formerly used as a pesticide to control insects, rodents, and birds. It has not been produced or sold for general use in the USA since 1986.

Acute human exposure to Endrin has demonstrated severe nervous system toxicity. Other acute signs of toxicity include: hyperexcitability, seizures, convulsions, and dizziness. Chronic signs of toxicity include: intermittent muscle twitching, psychological disorders, loss of consciousness and convulsions. There is also evidence of developmental effects in rodents.

As with other cyclodiene pesticides, the persistence of endrin in the environment depends highly on local conditions. It is estimated that endrin residues may in some instances persist in soil for more than a decade. Exposure to light, or to high temperatures, can also partially degrade endrin to form the closely-related compounds, endrin aldehyde and endrin ketone. Endrin has been found in many foods, but current levels appear to be very low and not of concern for human health. Because of its environmental persistence and its potential to bioconcentrate in aquatic organisms, there has been continued concern as to levels of endrin in fish and shellfish. However, this concern is limited largely to specific sites where endrin was used heavily in agriculture or was discharged by industrial point sources. In 1963, at the height of endrin's agricultural use, levels in catfish poisoned by endrin exceeded 4 ppm during a fish kill. Several more recent national studies, however, indicate that contaminated fish or shellfish are no longer a likely source of potentially high human exposure to this pesticide.

The oral RfD for endrin is 3E-4 mg/kg/day, and is based on a dog chronic oral bioassay study which observed mild histological lesions in the liver and kidney, and CNS effects. NOAEL from the dog study was 0.025 mg/kg/day.

LOAEL was 0.05 mg/kg/day. An uncertainty factor of 100 is used (10 fold uncertainty factor for extrapolation from animal to human, and another tenfold factor to account for uncertainty in the threshold for sensitive human populations.) Confidence is medium because the study was of average quality and reproductive data are lacking.

The weight of evidence for carcinogenicity is classified as D (not classifiable), based on findings that the oral administration of endrin did not produce carcinogenic effects in either sex, of two strains of rats and three strains of mice.

Endrin Aldehyde: CASRN 7421-36-3

This compound is a breakdown product, and an impurity, of Endrin. Only one available study was found for this compound, which demonstrated liver dysfunction in rodents. There is no oral RfD or carcinogenicity slope factor for this compound listed on IRIS or HEAST.

Endrin Ketone: CASRN 53494-70-5

This compound is a photodegradation product of Endrin, for which there is currently neither an oral RfD nor a carcinogenicity slope factor. Only one study could be found for this compound. It demonstrated liver dysfunction in rodents.

Heptachlor: 1,4,5,6,7,8,8-heptachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene; CASRN 76-44-8.

Heptachlor and Heptachlor Epoxide are cyclodiene pesticide residues, which are closely related to Chlordane. Heptachlor is also frequently a component of technical chlordane (at about 10 per cent). There are no natural sources of heptachlor or heptachlor epoxide. From the early 1950's until the mid-1970's, heptachlor was used to kill insects on seed grains, as well as various food crops. During this period it was also used by both homeowners and professional exterminators to kill termites. It has also been extensively used to kill fire ants.

Organochlorine pesticides such as these, are neurotoxicants for which acute signs of toxicity include: hyperexcitability, seizures, convulsions and dizziness. Chronic signs of toxicity include: intermittent muscle twitching, psychological disorders, loss of consciousness and convulsions. Primary toxicological endpoints for heptachlor are the central nervous system (CNS) and the liver.

Heptachlor has an oral RfD of 5E-4 mg/kg/day, which is based upon a two-year rat feeding study. Critical effect was liver weight increases in males; also hepatocellular swelling and peripheral arrangements of centrilobular cytoplasmic granules. The NOAEL from this study was 0.15 mg/kg/day. LOAEL (which IRIS describes as the “lowest effect level” (LEL) was 0.25 mg/kg/day. An uncertainty factor of 300 is used to account for interspecies and intraspecies differences (subfactor of 100) and to account for the lack of chronic toxicity data in a second species (subfactor of 3). However, the dog and rat are known to be somewhat similar in

sensitivity to this general group of cyclodiene pesticide compounds (see IRIS). Confidence in the RfD is low, due to the low overall quality of the supporting data, and incompleteness of the chronic toxicity information.

The oral cancer slope factor for Heptachlor is 4.5E+0 mg/kg/day. The weight of evidence for carcinogenicity is classified as B2; there is inadequate human data, but sufficient evidence exists from animal studies in which both benign (hepatic nodules) and malignant (hepatocellualr carcinomas) liver tumors were induced in three strains of mice of both sexes.

Heptachlor Epoxide: 1,4,5,6,7,8,8a-heptachloro-2,3-epoxy-3a,4,7,7a-tetra-hydro- 4,7-methanoindene; CASRN 1024-57-3

Heptachlor epoxide is not commercially available in the United States. It is not produced or applied as a pesticide, *per se*. Rather, it is an oxidation breakdown product of Heptachlor, and is present in the environment and in biological samples as a result of the prior or historic use of Heptachlor. Heptachlor epoxide is somewhat more potent toxicologically than heptachlor. Like heptachlor and other cyclodienes, it is neurotoxic, and hepatotoxic. Symptoms of acute poisoning include central nervous system (CNS) stimulatory effects, as with the other cyclodienes.

The oral RfD for heptachlor epoxide is 1.3E-5 mg/kg/day, taken from a 60 week dog feeding study, and based on increased liver-to-body weight ratios in both male and female animals. LOAEL (IRIS calls it a "LEL" in this instance) was 0.0125 mg/kg/day. No NOAEL was established form this particular study.

Uncertainty factor is 1000, due to inter and intra species differences (100 subfactor) and to account for the fact that no NOAEL was attained (10-fold subfactor). Confidence in the RfD is low. A 2-generation study in orally dosed dogs also resulted in reproductive toxicity, with pup survival as the critical effect. The reproductive NOEL for this endpoint was 0.125 mg/kg/day, which is ten times the level of the LOAEL derived for the endpoint of liver toxicity. "LEL" for reproductive toxicity was 0.175 mg/kg/day.

For carcinogenicity, Heptachlor epoxide has been classified as B2 (possible human carcinogen), based on findings of liver carcinoma in laboratory dosing studies of two strains of mice of both sexes; also in female rats. The cancer slope factor for Heptachlor epoxide is 9.1E+0 mg/kg/day.

Additional evidence for carcinogenicity of both heptachlor and heptachlor epoxide is provided by the fact that several other structurally related compounds in the cyclodiene group are known to be liver carcinogens.

Hexachlorobenzene (HCB): CASRN 118-74-1

Hexachlorobenzene does not occur naturally. It is found as a by-product of various industrial and manufacturing processes involving chlorine-containing compounds. It was also formulated to be used as a pesticide. From the late 1940s until the 1950s, it was extensively used as a fungicidal dressing on seed grains. Until about 1965 it was widely used as a pesticide in the USA. At the present time, there are no commercial uses of HCB in this country. HCB has a half-life in soil of about three to six years. Because of its relative persistence and common occurrence in the environment, very low levels of HCB have been found as a fairly routine contaminant in the fatty tissues of people.

Like other chlorinated organics, the toxicological effects of HCB are primarily upon the nervous system, and the liver.

The oral RfD for HCB is 8E-4mg/kg/day, based on a 130 week, rat oral feeding study. The NOAEL for HCB was 0.08 mg/kg/day, with a LOAEL of 0.29 mg/kg/day. Critical effect was liver damage. Human evidence for the toxicity of HCB is well documented. In a massive epidemic in Turkey in 1955-1959, liver damage (porphyria cutanea tarda) and other adverse effects to multiple organ systems was extensively observed in a population of about 4000 Turkish citizens who accidentally suffered long-term dietary exposure to bread made from grains treated with HCB. Even though there are also an extensive number of high quality animal studies on HCB, confidence in the RfD is medium, with an uncertainty factor of 100 (based on two subfactors of 10, for inter and intra species variability). One source of uncertainty is that the primary animal study was not designed to specifically evaluate the same type of liver damage (porphyria) as was observed in humans. Also, the human data lacked accurate dose and exposure information.

In terms of possible carcinogenicity, HCB has been classified in Group B2 (possible human carcinogen. This is based on studies in three rodent species which indicate that the oral administration of HCB induces liver tumors (the primary target organ), as well as kidney and thyroid tumors. The oral carcinogenic slope factor for HCB is 1.6 E+0 mg/kg/day.

HEXACHLOROCYCLOHEXANE (HCH, formally called BHC), and Isomers:
Technical HCH: CASRN 608-73-1

Alpha HCH: 1-Alpha, 2-alpha, 3-beta, 4-alpha, 5-beta, 6-beta-benzene-*trans*-hexachloride; CASRN 319-84-6

Beta HCH: 1-Alpha, 2-beta, 3-alpha, 4-beta, 5-alpha, 6-beta-hexachlorocyclohexane; CASRN 319-85-7

Gamma HCH (Lindane): 1-Alpha, 2-alpha, 3-beta, 4-alpha, 5-alpha, 6-beta-hexachlorocyclohexane; CASRN 58-89-9

Delta HCH: 1-Alpha, 2-alpha, 3-alpha, 4-beta, 5-alpha, 6-beta-hexachlorocyclohexane; CASRN 319-86-8

Formerly known as Benzene hexachloride (BHC), Technical HCH is a mixture of several isomers. These include the alpha, beta, gamma, and delta isomers of HCH, although an epsilon isomer is also possible in the mix. Of these, only the Gamma HCH isomer is known to possess insecticidal properties, and is primarily a neurotoxicant, with secondary effects on liver and kidney. The gamma isomer of HCH is also known as the pesticide, Lindane. Typically, the Alpha isomer makes up about 65 per cent of technical HCH, while the Gamma HCH isomer constitutes about 10 to 15 per cent. The Beta isomer is the HCH metabolite /isomer which is most commonly found in biological tissues.

Like most other members of the organochlorine series, the HCH compounds are neurotoxicants, stimulatory to the central nervous system. Acute signs of toxicity include paresthesia, ataxia and dizziness. Chronic signs of toxicity include: anorexia, mild anemia, tremors, seizures, muscular weakness, hyperexcitability and nervous tension.

Gamma HCH (Lindane) is used on various crops as a seed treatment for control of wireworms and other soil pests. Additionally, one of its primary uses in the USA and abroad is as a topical treatment for head and body lice, and scabies.

At this time, no RfD is available for Alpha, Beta, or Delta HCH. However, Alpha and Beta

HCH isomers have demonstrated liver toxicity in chronic animal exposure studies. Also, the toxicities and target effects of technical HCH and Alpha-HCH are known to be quite similar. Information on the non-cancer effects of Delta-HCH is not extensive in the available literature.

The oral RfD for Gamma HCH (a.k.a. Lindane) is 3E-4 mg/kg/day, and is based on a rat subchronic oral bioassay study which demonstrated liver and kidney toxicity. Critical effects were liver hypertrophy and kidney tubular degeneration. NOAEL for this rat study was 0.33 mg/kg/day (females). LOAEL (for male rats) was 1.55 mg/kg/day. An uncertainty factor of 1000 is used to account for subchronic vs a chronic study (sub-factor of 10), for interspecies variation (sub-factor of 10), and to protect sensitive human subpopulations (also sub-factor of 10). Confidence in the RfD is medium.

For technical HCH (which is about 65 per cent Alpha-isomer) the weight of evidence for carcinogenicity is classified as Group B2 (probable human carcinogen), based on an increased incidence of liver tumors in four different strains of mice. The oral carcinogenicity slope factor for technical HCH is listed in IRIS at 1.8E+0 mg/kg/day.

Alpha-HCH is also classified as a Group B2 (probable human) carcinogen. Alpha-HCH has a cancer slope factor of 6.3E+0 mg/kg/day. which makes it theoretically somewhat more potent as a carcinogen than technical HCH.

Beta-HCH has the same carcinogenic slope factor potency as technical HCH (slope factor for cancer is 1.8E+0 mg/kg/day) but is classified as a Group C (possible human) carcinogen, rather than as Group B2. Basis for the slope factor and classification is an increase in benign liver tumors in chronic studies of mice fed the beta-isomer.

Evidence for the carcinogenic potential of Gamma-HCH–has recently been somewhat equivocal. (i.e, the Gamma HCH isomer was formerly ranked as a B2-C carcinogen by IRIS.) However, in the past few years this classification and associated slope factor (1.3E+0 mg/kg/day) have been removed from IRIS, and are under further review by EPA.) At this writing, however, HEAST does list the Lindane slope factor at 1.3E+0 mg/kg/day, based on rodent liver tumors, and this value will be utilized for the Gamma HCH/Lindane isomer throughout this assessment.

The Delta isomer of HCH is of course closely related structurally to the carcinogenic technical HCH, as well as to the (also carcinogenic) Alpha and Beta isomers. Despite this structural

similarity, the available experimental cancer data regarding the Delta isomer are sufficiently equivocal, that IRIS lists Delta-HCH in Group D (not classifiable as to carcinogenicity). Accordingly, the determination of any carcinogenic slope factor appears inappropriate with respect to this isomer.

Mirex: 1,1a,2,2,3,3a,4,5,5a,5b,6-dodecachlorooctahydro-1,3,4-methano-1H-cyclobuta[cd]pentalene; CASRN 2385-85-5

Mirex is a pesticide which is closely related structurally to the insecticide, Kepone (chlordecone). Mirex was primarily used in this country as a pesticide during the 1960s and 1970s, for control of the invasive "fire ant" in various Southeastern States. It has not been commonly used as a pesticide in the Pacific Northwest. From 1959 to 1972 it was also used as a flame retardant in plastics, rubber, paint, paper, and electrical goods. It has not been manufactured or used in the USA since the late 1970s.

In animal studies, Mirex has been shown to cause multiple harmful effects on various organ systems, including the liver, kidneys, nervous system, thyroid, and digestive and reproductive organs.

The Oral RfD for Mirex is 2E-4 mg/kg/day, based on a rat chronic feeding study. Critical endpoints were liver enlargement, fatty liver and other hepatic changes. Cystic thyroid follicules and angiectasis (vessel dilation) were also noted as critical effects. Uncertainty factor is 300, which reflects 10 for intraspecies variability, 10 for interspecies extrapolation and 3 for lack of a multigenerational data on reproductive effects and cardiovascular toxicity data. Despite this, confidence in the RfD and the available toxicologic database is high, because of the availability of several high quality animal studies.

At this time, inadequate data are available as to potential carcinogenicity of Mirex, and this endpoint has not been fully clarified by EPA. IRIS has previously listed an oral carcinogenic slope factor of 1.8E+0 mg/kg/day for Mirex, but this number has been withdrawn. EPA has classified Mirex as a Group D (unable to classify as to carcinogenicity).

Pendimethalin: N-(1-ethylpropyl)-3,3-dimethyl-2,6-dinitrobenzenamine; CASRN 40487-42-1

Pendimethalin is a dinitroaniline compound, used as a pre-emergent herbicide. Although its

acute oral toxicity to mammals is usually low, pendimethalin is reported to be irritating to skin and eyes. A 1984 Purdue University fact sheet indicates that it is highly toxic to coldwater fish, highly to moderately toxic to warmwater fish, and highly to moderately toxic to freshwater invertebrates. Degradation in the environment is fastest under flooded, anaerobic conditions. The environmental persistence of pendimethalin in flooded soils like rice fields can be as brief as 3 to 7 days. However, in aerobic soils, the half-life of this pesticide can be as great as 28 to 172 days.

The oral RfD for pendimethalin is 4E-2, taken from data generated from a 1979 feeding study in dogs. The NOAEL was 12.5 mg/kg/day, based on an increase in serum alkaline phosphatase enzymes, increased liver weights, and liver lesions. The uncertainty factor for this RfD is 300, which includes a factor of 3 to account for the lack of an acceptable long-term study in a second species. A factor of 100 is also applied, to account for uncertainty in inter and intra-species differences. Confidence in the RfD is medium.

At this time, pendimethalin has not been evaluated by EPA/IRIS as to evidence of potential carcinogenicity.

Propargite: 2-(4-(1,1-dimethylethyl)phenoxy)cyclohexyl-2-propynyl sulfite;
CASRN 2312-35-8

Propargite is an acaricide with residual killing action, used primarily for control of spiders and mites. It is manufactured as a pesticide, under the product name, "Omite", and various other commercial preparations.

The oral RfD for propargite is 2E-2 mg/kg/day. This is based on two co-critical studies cited in IRIS. The first study was a two year oral feeding study in dogs. At the highest tolerated dose, no observable adverse effects were evident in the dogs, and no LEL was established. From these results, it was assumed that the NOAEL from this study was equal to or greater than the highest daily dose of 22.5 mg/kg/day. From this study, an uncertainty factor of 1000 is applied. The same oral RfD–2E-2 mg/kg/day, based on reproductive endpoints--was also calculated independently in IRIS from a 1982 oral dosing reproductive study of pregnant female rabbits. Here, a NOAEL of 2 mg/kg/day was observed, and the LEL was 6 mg/kg/day. Specific toxicologic endpoints in this rabbit study were maternal and fetal toxicity. Critical toxicologic effects included reduced maternal body weight gain and reduced body weight, as well as delayed

fetal ossification. Uncertainty factor for this study was 100. The use of two co-critical supporting studies for the RfD in IRIS was largely due to the irritating properties of propargite, and the gavage nature of the rabbit study, which makes it difficult to interpret conclusively the dose-related findings for the maternal and reproductive endpoints. Confidence in the RfD is medium, because of the lack of sufficient additional experimental data from chronic animal bioassays.

At this time, propargite has not been evaluated in terms of carcinogenic potential.

Triallate: 2,3,3-trichloroallyl,N,N-diisopropylthiocarbamate; CASRN 2303-17-5

Triallate is a pre-emergence selective herbicide, and is the active ingredient in the commercial product, "Far-Go", used on a variety of wheat, barley, pea and lentil crops. The oral RfD for triallate is 1.3E-2 mg/kg/day, based on a 1970 two-year feeding study in dogs. The NOAEL from this study was 1.275 mg/kg/day, with a LOAEL of 4.25 mg/kg/day. Critical toxicologic endpoints included increased hemosiderin deposition, especially in the spleen, as well as increased serum alkaline phosphatase levels and increased liver weights, in mid-dose and high-dose females. Uncertainty factor is 100, to account for inter and intraspecies differences. Confidence in the RfD is medium.

At this time, triallate has not been evaluated for potential carcinogenicity.

Trifluralin: 4-(di-N-proplyamino)-3,5-dinitro-1-trifluoromethylbenzene; CASRN 1582-09-8

Trifluralin is a selective pre-emergence herbicide, which is used on a wide variety of food crops. It is the active ingredient in the commercial product, "Treflan".

The oral RfD for trifluralin is 7.5E-3 mg/kg/day, based on a twelve month dog feeding study, published in 1984. NOAEL from this study was 0.75 mg/kg/day, with a LEL of 3.75 mg/kg/day. Critical toxic endpoints included increased liver weights, and increase in methemoglobin. An uncertainty factor of 100 is applied to this RfD to account for inter and intra-species differences, and confidence in the RfD is high, because the critical study is judged to be of good quality. Also, there are several other studies in other species which are supportive of the RfD.

Carcinogenicity: Trifluralin is classified in IRIS in Group C (possible human) carcinogen. This is based on the induction of tumors of the urinary tract (renal pelvis carcinomas and urinary

bladder papillomas), and of the thyroid (adenomas and carcinomas) in a 1980 chronic rat bioassay. In addition, trifluralin is structurally similar to the known rat carcinogen, ethylfluralin. The oral carcinogenic slope factor for trifluralin is 7.7E-3 mg/kg/day.

Toxaphene: CASRN 8001-35-2

Toxaphene is not a single compound, but is a mixture of various chlorinated camphenes. ATSDR indicates that toxaphene contains over 670 different individual chemicals. In 1982, EPA cancelled most of the uses of toxaphene, and in 1990, all uses of toxaphene in the USA were banned. Prior to 1982, toxaphene was one of the most heavily used insecticides in the USA. It was used primarily in the southern United States, for controlling insects on cotton and other crops. It was also commonly used as a "dip" to control insect pests on livestock, as well as to kill unwanted fish in lakes.

Toxaphene breaks down very slowly in the environment, and because of its many different ingredients, is not easy to analyze for in environmental samples. Toxaphene is broken down in the body somewhat more easily than most of the other organochlorines, and is excreted in urine and feces. However, studies in animals show that low levels of toxaphene may remain in fat for months. Remant concentrations of toxaphene as a hazardous waste are also still important. Even as recently as 1998-99, toxaphene was strongly implicated by EPA as a major contributing factor to a massive bird die-off near a Florida lake. Although toxaphene is the major suspect, dieldrin, chlordane, DDD and DDE are among the pesticides that were detected, often in high concentrations in the soils and bird tissues. It is likely that this particular toxaphene exposure was due to illegal dumping of old stocks of pesticide.

Exposure to high levels of toxaphene has been reported to damage the lungs, nervous system, liver, and kidneys, and can cause death. The severity of effects depend on how much dose is acquired. Studies in animals show that long-term exposure to toxaphene can damage the liver, kidneys, adrenals glands and immune system, and may cause minor changes in fetal development. Because toxaphene is no longer used in this country, the chances of high-level exposure are small. However, exposure to low levels can occur in some areas because of toxaphene's relatively significant environmental persistence.

At this time, IRIS has not developed an oral RfD for Toxaphene.

IRIS does list an oral carcinogenic slope factor of 1.1E+0 mg/kg/day, for toxaphene. With respect to carcinogenic potential for toxaphene, IRIS lists it as a Group B2 (possible human) carcinogen.

Phenol: hydroxybenzene; CASRN 108-95-2

Phenol, also known by the common product name of carbolic acid, is a chemical which is produced and utilized in many manufacturing processes and products. Phenol is extensively manufactured and used as a chemical intermediate, in the production of phenolic resins, nylon and other synthetic fibers, and epoxy resins.

Phenol also occurs naturally in the environment, in various living organisms. In humans, it is produced in small quantities and excreted independent of external exposure to the compound. It is thus commonly found in the urine of children and adults. The normal range of phenol in the urine of unexposed individuals is 0.5 to 80 milligrams of phenol per liter mg/L, or ppm) of urine. It is also found in nature in some foods, and in human and animal wastes and decomposing organic matter. Phenol is also present in many consumer products like ointments, ear and nose drops, cold sore lotions, mouthwashes, throat lozenges and antiseptic lotions. It has been found in drinking water, as well as foods like summer sausage, fried chicken, cheese, and some species of fish. The natural presence of phenols in food and drug metabolites (e.g., phenol is a by-product of salicylate metabolism) limits biological monitoring in people.

Phenol acts toxicologically as a general protoplasmic poison that denatures proteins and produces chemical burns characterized by a whitish or brownish area, especially on mucosal surfaces. Even though a 10 per cent solution can cause chemical burns, local effects tend to be more mild than those of strong acids or bases. Severe phenol exposures can result in seizures, respiratory arrest, heart arhythmias, and metabolic acidosis. The lethal oral dose in humans is 10-30 grams, although fatalities have occurred after ingestions of as little as 4.8 grams. The consumption of 0.6 grams has produced no symptoms. Phenol is absorbed rapidly through the lungs and skin. Children have died after the application of 5 per cent phenol compresses to the skin. Most absorbed phenol is biotransformed by the liver to various conjugated metabolites, which are rapidly excreted by the kidney. Elimination is nearly complete within 24 hours.

The oral RfD for phenol is 6E-01, with an uncertainty factor of 100. Critical toxicologic endpoint was reduced fetal body weight in rats, with a NOAEL of 60 mg/kg/day, and a LOAEL

of 120 mg/kg/day. An uncertainty factor of 100 is applied to the RfD, which includes 10 for interspecies extrapolation and 10 to account for sensitive human populations. Confidence in the RfD is low.

In terms of classification as to possible human carcinogenicity, EPA has assigned phenol a weight-of-evidence classification of Group D (not classifiable as to human carcinogenicity). This is based on the absence of any human carcinogenicity data, and inadequate cancer data in animal studies. Although some older studies indicate that phenol may be a promoter and/or weak skin carcinogen in specially inbred sensitive mouse strains, NCI concluded in a 2-year carcinogenicity bioassay of mice and rats that under the study conditions, phenol was not carcinogenic in either rodent species.

CHLOROPHENOLS:

The chlorophenols are a group of chemicals in which between one (mono-chloro) and five (penta-chloro) chlorine molecules have been added to a molecule of phenol. In all, there are 19 different chlorophenols. Six of these will be considered in this report.

Many of the various chlorophenols either have been used directly as pesticides, or have been converted into pesticides. Also chlorophenols, especially 4-chlorophenol, have been used as antiseptics. In addition to their commercial production, small amounts of some chlorophenols–especially the mono and dichlorophenols–when drinking water or waste water containing certain organic materials is disinfected with chlorine. Chlorophenols are also produced in the production of paper; i.e., when chlorine is used to bleach wood pulp.

Most chlorophenols released in the environment go into water, with relatively low quantities entering the air. Chlorophenols will photodegrade. In water, chlorophenols tend to adsorb to sediment. They can and do enter the aquatic food web, but–depending on the degree of chlorination–are normally broken down by microorganisms, with a persistence in the environment ranging from a few days to several weeks. Higher chlorinated species like penta and tetracholorophenol are an exception to this pattern, and can sometimes persist for longer periods, depending on the specific conditions at hand.

2-Chlorophenol: 2-chloro-1-hydroxybenzene; CASRN 95-57-8

All of the monochlorophenols have been used as biocides of one fashion or another, at various times in the past. The monochlorophenols have also been used as antiseptics, although in this role they have been largely replaced by other chemicals. The most common use of the monochlorophenols has been as chemical intermediates in the production of higher chlorinated phenols.

The oral RfD for 2-chlorophenol is 5E-3 mg/kg/day, with reproductive effects in the orally dosed rat as the critical toxicological endpoint. The NOAEL from these studies was 5 mg/kg/day, and the LOAEL was 50 mg/kg/day. Confidence in the RfD is low, with an uncertainty factor of 1000.

At this time, EPA has not evaluated 2-chlorophenol as to likelihood of carcinogenicity.

4-Chlor-3-methylphenol: 4-chloro-3-methyl-1-hydroxybenzene; CASRN 59-50-7

At this time, EPA has not established an RfD for this chemical, nor has it evaluated it as to likelihood of carcinogenicity.

2,4-Dichlorophenol (2,4-DCP): 2,4-dichloro-1-hydroxybenzene; CASRN 120-83-2

2,4-dichlorophenol has had pesticidal uses at various times in the past, as a miticide and for mothproofing. One of the most extensive uses of 2,4-DCP has been as a chemical intermediate, in the production of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). 2,4-D herbicide remains one of the most commonly used pesticides in the world, and is still extensively utilized in the U.S.

In sufficiently high doses, 2,4-dichlorophenol can cause toxicity to the liver and central nervous system (CNS). The oral RfD for 2,4-dichlorophenol is 3E-3 mg/kg/day, based on a decrease in the delayed hypersensitivity response in the orally dosed rat. NOAEL for this endpoint was 0.3 mg/kg/day, with a LOAEL of 3.0 mg/kg/day. Confidence in the RfD is low, with an uncertainty factor of 100.

At this time, 2,4-dichlorophenol has not been fully evaluated by EPA for possible carcinogenicity.

2,4-Dimethylphenol: 2,4-dimethyl-1-hydroxybenzene; CASRN 105-67-9

The oral RfD for 2,4-dimethylphenol is listed in IRIS as 2E-2 mg/kg/day. This is based on a subchronic (90 day) oral gavage study in the mouse. Critical toxic endpoints were hematological changes, and clinical signs of ataxia, lethargy and prostration in the animals. NOAEL from this study was 50 mg/kg/day, and the LOAEL was 250 mg/kg/day. Confidence in the RfD is low, with an uncertainty factor of 3000. This reflects a factor of 10 each for inter and intraspecies variability, and an additional factor of 30 for lack of chronic data in a second species, and inadequate information about reproductive/developmental studies.

At this time, neither IRIS has not evaluated this chemical as to carcinogenicity.

2,4,5-Trichlorophenol (2,3,4-TCP): 2,4,5-trichloro-1-hydroxybenzene; CASRN 95-95-4

The largest use for (2,4,5-TCP) has been as a chemical intermediate in the production of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). However, because 2,4,5-T is also frequently contaminated with trace amounts of dioxin(s) as an unintentional by-product resulting from the manufacturing process, 2,4,5-T was taken off the market in the USA in 1985.

The oral RfD for 2,4,5-trichlorophenol is 1E-1 mg/kg/day, based on critical endpoint effects of liver and kidney pathology in orally dosed rats. NOAEL from this study was 100 mg/kg/day, with a LOAEL of 300 mg/kg/day. Confidence in the RfD is low, with an uncertainty factor of 1000.

At this time, EPA has not evaluated 2,4,5-trichlorophenol for possible carcinogenicity.

2,4,6-Trichlorophenol (2,4,6-TCP): 2,4,6-trichloro-1-hydroxybenzene; CASRN 88-06-2

2,4,6-TCP and the tetrachlorophenols have been used directly as pesticides, in the preservation of wood. But more commonly, 2,4,6-TCP has been used as a chemical intermediate in the production of higher chlorinated phenols; especially 2,3,4,6-tetrachlorophenol, and pentachlorophenol.

At this time, IRIS has not developed a specific RfD for this compound.

IRIS does list 2,4,6-trichlorophenol as a Group B2 (possible human) carcinogen. This is based on increased incidence of lymphomas or leukemias in male rats, and hepatocellular adenomas or carcinomas in male and female mice. The carcinogenic oral slope factor for 2,4,6-trichlorophenol is 1.1E-2.

2,3,4,6-Tetrachlorophenol: 2,3,4,6-tetrachloro-1-hydroxybenzene; CASRN 58-90-2

Although tetrachlorophenol has been marketed and used in the past as a fungicide, its primary source today is most likely as a biodegradation product of pentachlorphenol (PCP). It has been measured in low quantities in various environmental media and foodstuffs, as well as human tissue. However, limited data do indicate that environmental biodegradation of 2,3,4,5-tetrachlorophenol may occur both aerobically and anaerobically. The most important human exposure scenario for this chemical would likely be occupational exposure, which might occur via dermal or inhalation pathways at workplaces like pulp or paper mills, or sawmills where PCP is used. The available data lists a modeled bioconcentration factor (BCF) of 930 for this compound, which suggests that the potential for bioconcentration in aquatic organisms is high.

The toxic mechanism(s) of action for this compound are similar to those of the closely-related PCP (see PCP), and involve the inhibition of critical oxidative phosphorylation pathways within cells of a wide variety of organisms. Like other chlorophenols, it can affect several organ systems, especially the liver. Occupational exposures to tetrachlorophenol dust has been found to be irritating to the nose and throat of exposed workers.

The oral RfD for this chemical is 3E-2mg/kg/day, based on a 1986 oral subchronic study in rats. Critical toxicologic target endpoint was the liver, which showed centrilobular hypertrophy and increased weight. NOAEL for this study was 25 mg/kg/day, with a LOAEL of 100 mg/kg/day. An uncertainty factor of 1000 is applied to this RfD. This includes subfactors of 10 each, to account for interspecies and intraspecies variability, and for extrapolating a subchronic effect to its equivalent chronic level. Confidence in the RfD is medium.

At this time, 2,3,4,6-tetrachlorophenol has not been evaluated by EPA in terms of likelihood of carcinogenicity.

Pentachlorophenol (PCP): CASRN 87-86-5

PCP is the most commonly used chlorinated phenol, with a long history of use in the USA as a wood preservative, fungicide, and bactericidal agent. Degradation of PCP in the environment can also result in the formation of other closely related pollutants discussed in this report; the most important of which are 2,3,4,5-tetrachlorophenol and pentachloroanisole, as well as pentachloroguaiacol. In recent years, most of the uses of PCP have been restricted, because of the tendency for PCP to be contaminated with trace quantities of higher chlorinated dioxins, as a result of the manufacturing process.

PCP exerts its primary mechanism of toxic action by inhibiting a very general, and essential cellular mechanism known as oxidative phosphorylation. A wide range of phyla share this common biochemical pathway. For this reason, it has been used as an effective "pesticide" to control many different forms of life–from the very simple to the very complex. In both humans and animals, significant exposure to PCP, can harm the liver, kidneys, blood, lungs, nervous system, immune system, and gastrointestinal tract. Impurities are also present in PCP.

These can include various of the higher chlorinated dibenzo-para-dioxins, which in the historic sense, were unintentionally produced in varying quantities along with the PCP. Depending on the concentrations and the exposure circumstances, such impurities in PCP may contribute to some of its harmful effects.

PCP is metabolized by the body relatively quickly, and thus does not tend to bioaccumulate in the fashion of more lipophilic compounds like DDT or PCBs. PCP adsorbs to soils and sediments, but can be broken down by microorganisms, to form other compounds in the environment. It is also degraded by sunlight in air and surface waters. PCP is known to be present in fish, but tissue levels are usually low because it can be metabolized and excreted by these and most other vertebrates.

The Oral RfD for pentachlorophenol is listed in IRIS as 3E-2 mg/kg/day.

This is based on a rat oral chronic feeding study, with liver and kidney pathology as the critical toxic endpoints. NOAEL from this study was 3 mg/kg/day, with a LOAEL of 10 mg/kg/day. Confidence in the RfD is medium, with an uncertainty factor of 100.

EPA (IRIS) also lists pentachlorophenol as a Class B2 (possible human) carcinogen. This is based on statistically significant increases in the incidence of multiple biologically significant tumor types in mice. Histologically, these tumors included hepatocellular adenoma/carcinoma, pheochromocytoma/malignant pheochromocytoma, and hemangiosarcoma/hemangioma. The existing human database on PCP is inadequate, and largely uninformative, in terms of further clarifying the likelihood of potential human carcinogenicity of PCP.

The oral carcinogenic slope factor for pentachlorophenol is 1.2E-1.

Pentachloroanisole: pentachloromethoxybenzene; CASRN 1825-21-4

Pentachloroanisole is not produced commercially. The most probable environmental source of this material in the environment is from the microbial biotransformation (methylation) of the commonly used pesticide/biocide, pentachlorophenol (PCP). PCP can be methylated to the corresponding anisole, in such media as soil, sediment, or wood chips. TOXNET bibliographic sources indicate that pentachloroanisole is also capable of being biotransformed back into PCP. The literature also indicates that anaerobic environments favor PCP, while aerobic environments favor pentachloroanisole.

People are exposed to pentachloroanisole primarily via food–especially oils and fats, and ambient air. While not evident in FDA's Total Diet Studies, dietary exposure may occur from eating contaminated fish and fish products like fish liver oil. Other exposure may occur via skin contact with soil or wood products which have been treated with PCP. Pentachloroanisole has been detected in pine needles, presumably because of its prevalence as an air pollutant in areas which use much PCP. In Sweden, pine needles have been used as a monitoring tool to establish past use patterns of PCP.

In the general sense, the toxicity and mechanism(s) of action(s) of pentachloroanisole are similar to those of its parent chemical, PCP (see section on PCP). However, methylation of the chlorophenols makes them more polar, and less reactive in biological systems. Thus the extent of both acute and chronic toxicity of pentachloroanisole can be reasonably anticipated to be somewhat less than its chlorinated parent, PCP.

At this time, EPA has not developed an RfD for pentachloroanisole.

The toxicological literature indicates that several studies have been conducted with rodents, as to pentachloroanisole's possible carcinogenicity and/or mutagenicity. However, the available animal cancer data are somewhat equivocal, and have not been fully evaluated by EPA. At this time, EPA has thus not developed a weight-of-evidence classification, in terms of evaluating likely carcinogenicity of this chemical, nor has it developed a carcinogenic slope factor for pentachloroanisole.

CHLORINATED GUAIACOLS: ortho-methoxy-chlorophenols

Guaicol is ortho-methoxy phenol. Guaiacol *per se*, appears to be somewhat less toxic and corrosive as phenol, and has pharmacological properties quite similar to those of phenol. Chlorinated guaicols are thus closely related structurally to the chlorinated phenol group of chemicals. The environmental presence of residues of the various chlorinated guaiacols is commonly associated with pulp and paper mills which utilize chlorine in the paper bleaching process.

The toxicology of the chlorinated guaicols is likewise similar to that of the chlorinated phenols; i.e higher chlorinated guaicols uncouple oxidative phosphorylation in mitochondria. In terms of their cellular toxicity and mode of action, they thus tend in a very general sense, to resemble pentachlorophenol. Chlorinated guaiacols also appear to be metabolized in the body by the same degradation pathway as pentachlorophenol.

Detailed and specific toxicity data for many of the chlorinated guaicols are not available in the literature at this time. Likewise, at this time none of the chlorinated guaicols have been evaluated by EPA in terms of either developing specific RfDs for toxicity, or evaluating their likelihood of carcinogenicity.

4-Chloroguaiacol: 4-chloro-2-methoxy-phenol; CASRN 16766-30-6

3,4-Dichloroguaiacol: 3,4-dichloro-2-methoxy-phenol; CASRN 77102-94-4

4,5-Dichloroguaiacol: 4,5-dichloro-2-methoxy-phenol; CASRN 2460-49-3

4,6-Dichloroguaiacol: 4,6-dichloro-2-methoxy-phenol; CASRN 16766-31-7

3,4,5-Trichloroguaiacol: 3,4,5-trichloro-2-methoxy-phenol; CASRN 57057-83-7

3,4,6-Trichloroguaiacol: 3,4,6-trichloro-2-methoxy-phenol; CASRN 60712-44-9

4,5,6-Trichloroguaiacol: 4,5,6-trichloro-2-methoxy-phenol; CASRN 2668-24-8

Tetrachloroguaiacol: 3,4,5,6-tetrachloro-2-methoxy-phenol; CASRN 2539-17-5

This guaiacol is the most common chlorinated phenolic compound associated with the process of chlorine bleaching of wood pulp.

Retene: 1-methyl-7-isopropyl phenanthrene; CASRN 483-65-8

Retene is a compound commonly noted in aquatic environments as a waste product from wood pulp and paper processing. It is found in pine tar, and is also formed from the dehydrogenation of the structurally-related resin acid, abietic acid. Resin acids such as these are major toxicants found in most pulp and paper effluents, especially kraft pulp mill effluents. (See also Chlorinated Guaiacols).

Relatively little information exists as to the toxicity of retene to humans and animals. At this time, EPA has not evaluated retene in terms of deriving a RfD for non-cancer endpoints.

Likewise, EPA has not evaluated retene in terms of potential carcinogenicity.

POLYBROMINATED DIPHENYL ETHERS (PDBEs):

PBDEs have been used as flame retardants in a wide variety of consumer products. Their use has also significantly increased in various of the more modern electronic items, chiefly in electronic boards used in computers, television sets and radios. According to the World Health Organization (1994), PBDEs are used primarily in two kinds of formulations. These are the deca-bromodiphenylether (10 bromines on the molecule), and the product known as Bromkal 705DE, which is a mixture of the hexa, penta, and tetra-bromodiphenyl isomers.

The PBDEs are relatively "new" environmental contaminants, first documented as environmental residues in 1981, in Swedish samples of sea trout, pike, and eel. Since these findings, many other studies have confirmed their presence in various media, including sediment, sewage sludge, birds and bird eggs, and marine mammals. It is likely that food is the main exposure route for these compounds in humans, in which recent data indicate that lower brominated congeners appear to be the most abundant variety of the PBDEs sequestered. Depending on the sampling site and the type of species or media sampled, reported concentrations in the environment have ranged from 8-110,000 micrograms per kilogram.

At this time, the only RfD available for any of the PBDEs is for the decabromodiphenyl ether (aka "decabromodiphenyl *oxide*, decabromo*bi*phenyl ether, decabromo*bi*phenyl *oxide*, Bromkal 83-10DE, Bromkal 82-ODE", etc., CASRN 1163-19-5). Laboratory analysis for residues of decabromodiphenyl ether was not attempted in this report. However, IRIS lists an oral RfD of 1E-2 for this compound, based on a rat oral bioassay study published in different segments in 1973 and 1975. Chronic dosing at 1.0 mg/kg/day, the highest dose given over the full 2 year period--revealed no observable chronic toxic endpoints. This dose was adopted as the chronic NOAEL, with no chronic LAOEL being derivable from the 2-year data at hand. This same study also included a subset of separate oral dosing data from a 30 day time interval, using much higher daily doses. From this portion of the experiment, a short term to sub-chronic NOAEL of 8 mg/kg/day was derived, with the toxic endpoint of liver enlargement in the dosed animals. The sub-chronic LOAEL was 80 mg/kg/day. This subchronic NOAEL is close to the chronic NOAEL of 1.0 mg/kg/day when adjusted by a factor of 10 to account for the uncertainty in extrapolating subchronic dose to chronic dose. A uncertainty factor is applied to the chronic NOAEL to account for intra-and interspecies variability. Confidence in the oral RfD is medium.

Likewise at this time, the only PBDE species which has been evaluated by EPA/IRIS for carcinogenicity is decabromodiphenyl ether. EPA/IRIS has classified decabromodiphenyl ether in Group C (possible human carcinogen). This is based on no human data, and limited evidence of animal carcinogenicity. The animal data include significantly increased incidences of neoplastic liver nodules in male and female rats, and increased incidences of hepatocellualr adenomas or carcinomas (combined) in male mice.

At this time, no oral carcinogenic slope factor has been developed by EPA for decabromodiphenyl ether, nor have the various other PBDEs relevant to this report been evaluated by IRIS or EPA in terms of possible carcinogenicity.

Hexabromodiphenylether: CASRN 36483-60-0

In the present study, a total of 25 different fish samples, spanning 5 species, showed positive results for this compound. However, all of these positive individual analytical findings were accompanied by a "J" data qualifier (See QA Section). This means that the analyte was analyzed for and was positively identified, but (for various reasons, chief among which are the very low level of detection being sought, the relative degree of efficiency of the laboratory analytic techniques, etc.) the associated numerical value(s) may not be consistent with the amount actually present in the environmental sample.

At this time, no RfD has been developed for hexabromodiphenylether, nor has it been evaluated by IRIS or EPA in terms of possible carcinogenicity.

Pentabromodiphenylether: Bromkal 70; CASRN 60371-14-4

In the present study, a total of 45 different fish samples, spanning 6 species, showed positive results for this compound. However, all of these positive individual analytical results were accompanied by a "J" data qualifier (see QA Section). This means that the analyte was analyzed for and was positively identified. However, for various reasons, chief among which are the very low levels of detection being sought, the relative degree of efficiency of the analytical method, etc., the associated numerical value(s) may not be consistent with the amount actually present in the environmental sample in question.

At this time, no RfD has been developed for pentabromodiphenylether, nor has it been evaluated by IRIS or EPA for possible carcinogenicity.

Tetrabromodiphenylether: CASRN 40088-47-9

In the present study, a total of 55 fish samples, spanning 5 species, showed positive results for this compound. However, all of these positive individual analytical results were accompanied by a "J" data qualifier (See QA Section). This means that the analyte was analyzed for, and was positively identified. However, for various reasons–chief among which are the very low levels of detection being sought, the relative degree of efficiency of the analytical method, etc-the associated numerical values may not be consistent be consistent with the amount actually present in the environmental sample in question.

At this time, no RfD has been developed for tetrabromodiphenylether, nor has it been evaluated by IRIS/EPA for possible carcinogenicity.

MISCELLANEOUS OTHER ETHERS

4-Bromophenyl-phenylether: p-bromodiphenyl ether; CASRN 101-55-3

This chemical is not produced commercially in the USA, but has been detected in surface water, as well as in occasional finished samples of drinking water. The environmental sources of 4-bromophenyl phenyl ether are not clearly known at this time, but are thought to arise primarily from the chlorination treatment of sewage and drinking water. For example diphenyl oxide, a probable precursor to this chemical, can be released to various chlorination operations through its use as a common dye vehicle and as a heat exchange fluid; thus formation of 4-bromophenyl phenylether from this released diphenyl oxide may be a possibility.

4-bromophenyl phenylether has also been used in the past in various polymer materials, as a flame-retardant additive.

At this time, EPA has not developed a RfD for this chemical.

In terms of the likelihood of this chemical being a carcinogen, EPA has given 4-bromophenyl-phenylether a classification of Group D (not classifiable as to human carcinogenicity), due to the lack of human data, and the absence of adequate animal data. No

long-term animal studies of carcinogenicity are available.

4-Chlorophenyl-phenylether: p-chlorodiphenyl ether; CASRN 7005-72-3

4-chlorophenyl phenylether is a man-made compound, and is not known to exist in nature. It is manufactured and used as a dielectric fluid, to replace PCBs, and is used primarily in electrical capacitors. Probable routes of human exposure to this compound would be via inhalation and/or dermal contact, as a result of such manufacture, formulation, or use. Environmental release may likewise occur during production, use, or disposal.

The environmental persistence of 4-chlorophenyl phenylether is much less than that of its PCB predecessor compounds. The estimated atmospheric half-life is about 2.3 days, and the half-life with respect to biodegradation in activated sludge is approximately 4 hours. It is not considered to be a compound with high bioaccumulation potential, nor does the literature of which we are aware indicate that it has been detected in fish.

At this time, EPA has not established a RfD for 4-chlorophenyl phenylether.

As to the likelihood for potential carcinogenicity of this chemical, EPA has at this time not evaluated 4-chlorophenyl phenyl ether, in terms of carcinogenic weight-of-evidence, or other related factors.

bis(2-Chloroisopropyl)ether: CASRN 39638-32-9

This chemical has been occasionally detected in surface water and drinking water samples. It is not predicted to persist for long periods in environmental media. The TOXNET database indicates that the half life via volatilization for this chemical in a given water body is calculated at 1.37 days.

The RfD for this compound is listed in IRIS at 4E-2 mg/kg/day. This is based on a 2 year dietary exposure study in mice, with critical endpoints being noted on the hemopoetic system (hemoglobin decrease and possible destruction of red blood cells). NOAEL for this study was 35.8 mg/kg/day, with a LOAEL of 198 mg/kg/day. Confidence in the RfD is low, with an uncertainty factor of 1000 to account for both interspecies (factor of 10) and interhuman (factor of 10) variability in the absence of sufficient animal data (no second animal species, etc.) An

additional tenfold uncertainty factor was also added, due to data gaps in the evaluative studies which are available for this chemical.

EPA/IRIS has not at this time evaluated bis(2-chloroisopropyl) ether, in terms of weight-of-evidence for possible carcinogenicity. However, HEAST lists it as a Group C (possible human) Carconogen, with an oral carcinogenic slope factor of 7E-2 mg/kg/day. This is based on liver and lung tumors in rodents.

Hexachlorobutadiene: (HCBD), 1,1,2,3,4,4-Hexachloro-1,3-butadiene; CASRN 87-68-3

Hexachlorobutadiene is a man-made chemical generally present as a liquid at typical temperatures encountered in the environment. Hexachlorobutadiene is used as an intermediate in the manufacture of other chemicals (e.g., rubber compounds), as a hydraulic and heat transfer fluid and in gyroscopes (ATSDR, 1994). There is very little information on the potential mobility of hexachlorobutadiene in environmental media. The compound may accumulate in aquatic organisms living in affected surface waters. Exposure to this chemical may be determined by evaluating urine and blood for hexachlorobutadiene metabolites. However, due to the rapid metabolism and elimination of this compound, this will only provide an indication of very recent exposures. It may also be valuable to conduct kidney function tests to determine if exposure has resulted in impaired kidney function.

Human data on the health effects of hexachlorobutadiene exposure are extremely limited and existing studies are complicated by simultaneous exposures to other solvents. Data from studies in laboratory animals therefore provides most of what we know about hexachlorobutadiene toxicity. Hexachlorobutadiene has been shown to be absorbed after oral exposure in experimental animals, although the degree of absorption has not been clearly defined. Oral exposure to this chemical may lead to kidney damage in experimental animals and the kidney appears to be the primary target organ for toxicity. Some effects were also observed in the liver but these occurred at higher concentrations relative to the kidney effects (ATSDR, 1994). Similarly, hexachlorobutadiene exposure did result in developmental effects in experimental animals (decreased pup weights) but the toxic effect levels were above those reported to cause effects in the kidney.

Non-Cancer Health Risks: The oral RfD for Hexachlorobutadiene is listed in HEAST, as 2E-4 mg/kg/day, based on an oral 13-week study in mice. LOAEL was 0.5 mg/kg/day, and the critical

toxic endpoint was renal tubule regeneration. IRIS has withdrawn its oral RFD (in May, 1993) for hexachlorobutadiene, and indicates that a new RfD summary is in preparation. The ATSDR has established a Minimum Risk Level (MRL) of 0.0002 mg/kg/day, for intermediate duration exposures. This was derived from a finding of kidney degeneration in female mice at a dose level of 0.2 mg/kg/day for 13 weeks (NTP, 1991). This finding was supported by other studies showing similar findings at higher doses (e.g., 2 mg/kg) in both rats and mice.

Carcinogenesis: There is only limited evidence regarding the possible carcinogenicity of hexachlorobutadiene but this evidence suggests the chemical is a possible human carcinogen. IRIS lists hexachlorobutadiene in Class C (possible human carcinogen). This is based on a two year rat study, in which findings of renal tubular adenomas and carcinomas were noted in 18 per cent of the high-dosed females, with high dose males exhibiting significant mortality before the study was concluded. There was no significant increase in neoplasia at other tissue sites. There are currently no human studies on hexachlorobutadiene carcinogenicity. A single study (Kociba, 1977) indicated that hexachlorobutadiene caused increased kidney tumors in female rats. Increased tumor incidence was only observed in the high dose group, 20 mg/kg/day. The derived oral slope factor for HCBD is listed in IRIS at 7.8E-2 mg/kg/day.

References

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Hexachloroethane: perchloroethane; 1,1,1,2,2,2-hexachloroethane; CASRN 67-72-1

Hexachloroethane is a man-made chemical also known as perchloroethane, carbon hexachloride or HCE. Hexachloroethane may be present as an ingredient in certain pesticides, plastics, lubricants, cellulose and smoke producing devices. It is also used in the process of aluminum smelting. Hexachloroethane may be present in soil, water or air and may move readily between environmental media. Hexachloroethane has only a limited potential to accumulate in fish tissues since it is metabolized and eliminated quickly (ATSDR, 2000). Because of it's rapid metabolism and elimination, monitoring for exposure to this chemical may be difficult.

The degree to which hexachloroethane is absorbed in the GI tract will vary with the composition

of the material being ingested. Absorption values derived from animal studies have ranged from 19% (in rabbits) to 88% (in mice). Hexachloroethane distributes to most tissues and is eliminated fairly rapidly with a half life less than three days in rats (ATSDR, 2000). Hexachloroethane is excreted via urine, feces and exhaled air. Adverse effects of hexachloroethane exposure include liver toxicity and irritation of the eyes, nose and lungs after inhalation exposure. There is very limited data on the toxicity of hexachloroethane in humans, most knowledge comes from studies in experimental animals. Hexachloroethane has not been reported to cause developmental effects in either humans or animals, although the number of studies examining this endpoint is limited.

Non-Cancer Health Risks: IRIS lists an oral RfD of 1E-3 mg/kg/day, for hexachloroethane. This is based on a subchronic dietary study in the rat (Gorzinski et al, 1985), in which male rats exhibited renal lesions consisting of atrophy and degeneration of the renal tubules. NOAEL for this study was 1 mg/kg/day, with a LOAEL of 15 mg/kg/day. These findings were supported by several additional studies (IRIS, 2000). Confidence in the RfD is medium, with a uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for possible human sensitivity and 10 for the use of a subchronic study).

Developmental and reproductive effects have also been observed for hexachloroethane but these were observed only at concentrations (e.g., 500 mg/kg) higher than the kidney effects used to determine the RfD (IRIS, 2000). The level of confidence ascribed to the RfD is described as medium due to the limited number of animals and limited time duration of the Gorzinski et al study.

Carcinogenesis: There is only limited evidence regarding the possible carcinogenicity of hexachloroethane. There are currently no human studies on hexachloroethane carcinogenicity. For classification as to evidence of potential carcinogenicity, IRIS has placed hexachloroethane in Group C (possible human carcinogen). This is based on an oral dosing study (NCI, 1978) which indicated that hexachloroethane caused increased liver tumors in mice, but not in rats. Mice of both sexes showed significant increase in hepatocellular carcinoma. The doses in these studies were high, 200-400 mg/kg/day in rats and 600-1200 mg/kg/day in mice. The derived oral slope factor is listed in IRIS at 1.4E-2 mg/kg/day.

References

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POLYCHLORINATED BIPHENYLS (PCBs):

PCBS are a group of synthetic organic chemicals that contain 209 individual chlorinated biphenyl compounds (known as PCB congeners). There are no known natural sources of PCBs in the environment. Their chemical structures–which often contain numerous chlorine atoms at various critical sites on the biphenyl ring, are difficult to thermally degrade, unless high temperatures are involved. PCBs do not conduct electricity, and most of the various types of PCBs and PCB mixtures take the form of liquids. For these reasons, PCBs have been used extensively in much of the world as electrical insulating fluids, especially in capacitors and transformers which deliver high voltage in critical devices and situations where fire prevention is of great concern. PCBs have also been used extensively as hydraulic fluids, as well as in the manufacture of carbonless copy paper, etc.

Unfortunately, such industrially useful chemical and physical properties also means that PCBs are extremely persistent and difficult to degrade in the environment. PCBs enter the environment as mixtures containing a variety of individual components (congeners) and impurities that vary in toxicity. The chlorinated nature of the various PCB molecules also makes them more fat soluble, and thus capable of bioaccumulating upward in various food webs, especially in aquatic environments. Such chlorination of the PCB molecules also makes it quite difficult for organisms to degrade and excrete them by usual biochemical pathways. The historic dumping, and leakage, of PCB waste oils over the past few decades has made them major environmental contaminants on a global scale. The manufacture, processing and distribution in commerce of PCBs in the United States was restricted beginning in October 1977, because of these harmful effects on the environment.

Commercially available PCB mixtures are known in the United States by their industrial trade

name, “Arochlor”. Each Arochlor mixture is further identifiable by a specific number; i.e., “Arochlor 1242". The “12" portion of this designation refers to the fact that the molecule contains 12 carbon atoms (bound together in two six-sided phenyl rings; e.g., a “biphenyl”). The “42" portion refers to the per cent of chlorination in the mixture. In terms of analytical laboratory capabilities, up until the 1990's most PCB residues in the environment were usually analyzed and expressed in terms of the various “arochlors”-such as 1242, 1254, 1260-etc, rather than as the specific PCB congeners.

Congener analysis is a more intensive, and expensive process, and has only been developed relatively recently. However, congener analysis provides the most information about risk, because this type of analysis allows one to know the specific structural characteristic of the individual PCB molecule(s) detected, and how closely they may or may not biologically mimic the cellular activity of TCDD dioxin, which is the toxicological benchmark used in predicting the extent and severity of PCB congeners as they might affect living organisms.

Toxicity: Despite this wide spectrum of non-degradability, environmentally undesirable properties, and highly sophisticated risk assessment models for specific dioxin-like PCB congeners, unless relatively high doses are involved, PCB acute toxicity is usually low to moderate with few clinically observable symptoms. However, chronic toxicity is extremely important, because many specific PCB congeners–due to their co-planar shape and specific configuration(s) of chlorine atoms-are capable of interacting with cellular receptors in the same fashion as “dioxin”. (See subsequent discussion section on PCB congeners; see also Dioxins and Furans). Mechanistic studies have recently identified several PCB congeners which demonstrate significant dioxin-like activity, and thus might promote tumors by different modes of action. (See profiles for specific PCB congeners, and for Chlorinated Dibenzodioxins, and for Chlorinated Dibenzofurans). PCB congeners which are not co-planar are also toxic, but exert their effects via a different cellular mechanism.

Carcinogenicity: PCB arochlors–like most other environmental toxicants–are assessed for potential cancer risk by means of their individual carcinogenic slope factors. The specific and chemically unique PCB congeners, on the other hand, lack individual slope factors, *per se.* Rather, PCB congeners are assessed for cancer potential on the basis of how closely their individual structure(s) resemble the co-planar structure and specificity of chlorination of the closely related dioxin molecule, 2,3,7,8-Tetrachlorodibenzo-p-dioxin. (See also discussions of

carcinogenicity assessment, for specific PCB arochlors and congeners and for chlorinated dioxins and furans).

Environmental alteration of PCBs; toxicological significance: With respect to the various mixtures of persistent and bioaccumulative PCB arochlors and congeners, it is important to remember that once in the environment, they are altered over time by various physical and biological processes of partitioning, chemical transformation and preferential bioaccumulation. Such processes in the environment can thus considerably alter the toxicity of the original PCB mixture, by either increasing or decreasing potency due to changes in the shape, and/or extent of chlorine substitution of the biphenyl rings.

Environmental partitioning can cause different portions of a PCB mixture to be encountered through various exposure pathways; *i.e.*, the fraction of the original PCB mixture which adsorbs to sediment or soil tends to be higher in chlorine content than the original mixture. It also tends to be more difficult for organisms to biotransform and eliminate by metabolic processes. Such PCB fractions would thus be higher in persistence, and possibly toxicity as well. Consequently, ingesting PCB-contaminated sediment or soil, or inhaling contaminated dust could theoretically pose a somewhat higher risk (than for example, ingesting PCB contaminated drinking water or breathing ambient air). This is because the PCB mixture fraction which dissolves in water or evaporates into air in the environment tends to be lower in chlorine content and persistence, and thus would likely pose lower risk upon inhalation of evaporated congeners, or ingesting water soluble congeners from the original mixture.

Not surprisingly, bioaccumulated PCBs are of the greatest concern because they appear in general to be more toxic than commercial PCBs and more persistent in the body. Accordingly, current techniques in assessing risk from PCBs utilize toxicity studies of commercial mixtures to develop a range of cancer potency estimates, and then consider the effects of environmental processes to choose appropriate risk values for representative classes of environmental PCB mixtures.

"Endocrine Disruption": In addition to considerations of their various frank toxicologic endpoints and potential carcinogenicity, PCBs have also been investigated during recent years as potential endocrine disruptors. (EPA has defined an endocrine disruptor as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, development, and/or behavior". There is at present much scientific debate as to whether environmental

chemicals acting via such endocrine disruptor mechanisms are responsible for adverse health effects in humans. Because humans have intrinsic physiologic feedback mechanisms to control the fluctuations of hormone levels, exposures to chemicals at the levels found in the environment may be insufficient to disrupt endocrine homeostasis. Current screening assays which measure hormone receptor binding thus may or may not be associated with an actual or observable corresponding adverse health effect. Moreover, exposures to potential environmental endocrine disruptors are minimal, compared to exposures to potential endocrine disruptors which occur naturally in food. However, it is also possible that infants and children are more sensitive to potential endocrine disruptor effects during sensitive periods of development.

PCB Arochlors: As outlined previously in this discussion, PCB Arochlors are mixtures of chlorinated congeners, with the last two digits indicating the percentage of chlorine in the compound (i.e., 42% for Arochlor 1242 and 54% for Arochlor 1254).

Non-Cancer effects: Of the various PCB Arochlors, IRIS has at this time derived oral reference doses (RfD) for only two; Arochlor 1016 and Arochlor 1254. However, both RfDs are derived from laboratory studies of primates, rather than from rodents. Respective uncertainty factors for both RfDs are thus relatively low (100 and 300, respectively). The oral RfD for Arochlor 1016 is 7.0E-5 mg/kg/day, based on monkey reproductive bioassays, with a critical toxicologic endpoint of reduced birth weights. For Arochlor 1254, IRIS lists an oral RfD of 2E-5 mg/kg/day, based on ingestion studies in the Rhesus monkey. Various other studies have indicated potential neurobehavioral deficits in primates, and adverse effects on the gastrointestinal, hematological, musculoskeletal, hepatic, renal, immunological and reproductive systems in humans and animals exposed to PCB mixtures. PCBs are absorbed through ingestion, inhalation, and dermal exposure, after which they are transported similarly through the circulation. This provides a reasonable basis for expecting similar internal effects from different routes of environmental exposure. Information on relative absorption rates suggests that differences in toxicity across exposure routes are small.

Cancer effects: Certain PCB Arochlors--1016, 1242, 1254 and 1260--have been classified by IRIS as B2 (probable human) carcinogens, based upon a 1996 study which found liver tumors in female rats exposed to these four Arochlors. These dosage mixtures contain overlapping groups of PCB congeners that, together, are currently thought to span the range of congeners most often found in environmental mixtures. Earlier studies have found high, statistically significant

incidences of liver tumors in rats ingesting Arochlor 1260. EPA's IRIS database is currently updating the various available human studies. Currently available human evidence for carcinogenicity is inadequate, but suggestive.

It is important to note that because of their relatively well-characterized patterns of preferential partitioning across various environmental media, certain of the lower chlorinated PCB Arochlors; --especially 1016, 1221, and 1232--are not likely to bioaccumulate in fish tissue. Nor were these three PCB arochlors detected in any CRITFIC fish samples. Nonetheless, this study assigned these three arochlors with the more conservative choice of carcinogenic slope factors listed for various Arochlors (2E+0 mg. kg/day-1; see IRIS).

The PCB Arochlors considered in this report are as follow:

Arochlor 1016: CASRN 12674-11-12

As discussed previously, Arochlors 1016 and 1254 are the only two PCB Arochlors for which IRIS has derived RfDs. IRIS lists an Oral RfD of 7.0E-5 mg/kg/day for Arochlor 1016, based on a suite of various monkey reproductive bioassays conducted from 1984-1991. Critical effect was reduced birth weights, with a NOAEL of 0.007 mg/kg/day, and a LOAEL of 0.028 mg/kg/day. Confidence in the RfD is medium, with an uncertainty factor of 100. Within this, subfactors of 3 each are applied to account for sensitive individuals, for extrapolation from rhesus monkeys to humans, for limitations in the data base, and for extrapolation from a subchronic exposure to a chronic RfD.

In estimating the likely carcinogenic potential for this compound, EPA IRIS lists Arochlor 1016 as a Group B2 (probable human) carcinogen. This is based on a 1996 study which found tumors in rats orally exposed to Arochlors 1216, 1242, 1254, and 1260. The PCB dosage mixtures contained overlapping groups of specific PCB congeners that together span the range of congeners most often found in environmental mixtures. Significantly increased incidences of liver adenomas or carcinomas were found in female rats for all Arochlors tested, and in male rats for Arochlor 1260. Some of these tumors were hepatocholangiomas, a rare bile duct tumor seldom noted in control rats. In addition, for all Arochlors tested, male rats showed an increase in thyroid gland follicular cell adenomas or carcinomas.

Because of its lower degree of chlorination and relatively well-characterized patterns of

preferential partitioning across various environmental media, Arochlor 1016 is not likely to

bioaccumulate in fish tissue, nor was this arochlor detected at any level in any of the CRITFC fish samples. However, for this and other PCB Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS suggests a derived oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1221: CASRN 11104-28-2

No oral RfD is available for Arochlor 1221 at this time.

This lower-chlorinated arochlor is not expected to significantly bioaccumulate in fish tissue, nor was it detected in any of the CRITFC fish samples. However, for this and other PCB Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1232: CASRN 11141-16-5

No oral RfD is available for Arochlor 1232 at this time.

Arochlor 1232 is not expected to significantly bioaccumulate in fish tissue, nor was it detected in any of the CRITFC fish samples. However, for this and other PCB Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1242: CASRN 53469-21-9

No oral RfD is available for Arochlor 1242 at this time.

In terms of carcinogenic potential for this compound, IRIS lists Arochlor 1242 as a Group B2 (possible human) carcinogen. This is based on a 1996 study which found tumors in rats orally exposed to Arochlors 1242, 1016, 1254 and 1260. The PCB dosage mixtures contained overlapping groups of congeners that together span the range of congeners most often found in environmental mixtures. Significantly increased incidences of liver adenomas or carcinomas

were found in female rats for all Arochlors tested, and in male rats for Arochlor 1260. Some of these tumors were hepatocholangiomas, a rare bile duct tumor seldom noted in control rats. In addition, for all Arochlors tested, male rats showed an increase in thyroid gland follicular cell adenomas or carcinomas.

For PCB 1242 and other Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1248: CASRN 12762-29-6

No oral RfD is available for Arochlor 1248 at this time. The USEPA RfD/RfC Work Group deemed the database at the time of review to be insufficient to derive an oral RfD according to the current Agency guidelines. The status does not preclude the use of information in cited references for assessment by others (see IRIS). Derivation of an oral RfD for Arochlor 1248 is not recommended because a "frank effect" (death of an infant) was noted at the lowest dose tested in a sensitive animal species, the Rhesus monkey. In general, Rhesus monkeys have shown adverse effects to PCB mixtures at doses tenfold lower than in other species.

For PCB 1248 and other Arochlors associated with food chain exposures and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1254: CASRN 11097-69-1

As discussed previously, Arochlors 1254 and 1016 are the only two PCB Arochlors for which IRIS has derived RfDs at this time. The oral RfD for Arochlor 1254 is 2E-5mg/kg/day. This is based on data from clinical and immunological ingestion studies on Rhesus monkeys, conducted in 1989, 1991, and 1994. The LOAEL was defined as 0.005 mg/kg-day. No NOAEL was established in this study. Critical effects included oclular exudate, inflamed and prominent eyelid Meibomian glands, distorted growth of finger and toe nails, and decreased antibody (IgG and IgM) response. An uncertainty factor totaling 300 is used in this evaluation. It includes a 10-fold factor which is applied to account for sensitive individuals, and a factor of 3 which is applied because of the extrapolation from primates to humans. An additional tenfold factor was also included, due to inconsistencies in effect levels for reproductive toxicity in the available database.

Confidence in the RfD is medium due to inconsistencies in effect levels for reproductive toxicity.

In assessing potential carcinogenicity, IRIS lists Arochlor 1254 in Group B2 (probable human carcinogen). This is based on a 1996 study which found tumors in (especially female) rats orally exposed to Arochlors 1254, 1016, 1242 and 1260. The PCB dosage mixtures contained overlapping groups of congeners that together span the range of congeners most often found in environmental mixtures. Significantly increased incidences of liver adenomas or carcinomas were found in female rats for all Arochlors tested, and in male rats for Arochlor 1260. Some of these tumors were hepatocholangiomas, a rare bile duct tumor seldom noted in control rats. In addition, for all Arochlors tested, male rats showed an increase in thyroid gland follicular cell adenomas or carcinomas.

For PCB 1254, and other Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Arochlor 1260: CASRN 11096-82-5

No oral RfD is available for Arochlor 1260 at this time.

In assessing the potential carcinogenicity of this compound, EPA IRIS lists Arochlor 1260 in Group B2 (probable human carcinogen). This is based on a 1996 study which found tumors in rats orally exposed to Arochlors 1260, 1016, 1242 and 1254. The PCB dosage mixtures contained overlapping groups of PCB congeners that together span the range of congeners most often found in environmental mixtures. Significantly increased incidences of liver adenomas or carcinomas were found in female rats for all of the four Arochlors tested, and in male rats for Arochlor 1260. Some of these tumors were hepatocholangiomas, a rare bile duct tumor seldom noted in control rats. In addition, for all Arochlors tested, male rats showed an increase in thyroid gland follicular cell adenomas or carcinomas.

For PCB 1260 and other Arochlors associated with food chain exposure and other situations involving relatively high persistence and therefore higher risk, IRIS has recommended an oral carcinogenic slope factor of 2E+0 mg/kg/day.

Specific PCB Congeners: (see also discussion on chlorinated dioxins and furans)

The “PCB Arochlors” discussed above are in fact, complex mixtures of various individually distinct PCB molecules, each of which may vary considerably in terms of the specific structural location and extent of chlorination. Each molecule of such a PCB mixture has 10 positions which can be occupied by a chlorine atom.

The placement and number of chlorine atoms into these positions determine the physical and chemical properties–and the toxicological significance-of the specific PCB molecule in question. There are 209 different possible arrangements of the chlorines in the 10 available positions. Each unique arrangement is called a “PCB Congener”. The fate and biological activity of each PCB congener is thus highly influenced by the number and placement of chlorines. Of the 209 possible chlorinated PCB congeners, only 20 have non-ortho chlorine substitutions in the biphenyl rings. Because of this, these particular congeners–substituted in the para and meta positions--can attain a planarity which makes their structure similar to the highly toxic dibenzo-p-dioxins and dibenzofurans.

Especially important within this group of 20 PCB congeners are the PCB congeners having four, five, or six chlorines in non-ortho positions. For example, three such PCB congeners have shown to be significantly potent mimics of 2,3,7,8-TCDD and 2,3,7,8-TCDF, in terms of enzyme induction and toxic effects.

These three congeners of particular toxicological importance are:

PCB 77: (3,3'4,4'-tetrachlorobiphenyl) CASRN 32598-13-3

The Relative Potency Factor (compared to 2,3,7,8-TCDD dioxin) for PCB 77 is 0.0001.

PCB 126: (3,3',4,4',5-pentachlorobiphenyl) CASRN 57465-28-8

The Relative Potency Factor for PCB 126 is 0.1, which is the highest TEQ yet assigned to any of the various dioxin-like PCB congeners.

PCB 169: (3,3',4,4',5,5'-hexachlorobiphenyl) CASRN 32774-16-6

The Relative Potency Factor for PCB 169 is 0.01.

Mono-ortho substitutions of chlorine on the biphenyl rings of these three toxic congeners can also exhibit significant toxicity. Such mono-ortho substitutions of (the tetra-chloro) PCB 77 yield the two penta-chloro PCB congeners, 105 and 118.

Similar mono-ortho substitutions of (penta-chloro) PCB 126 result in the formation of the three hexa-chloro PCB congeners 156, 157, and 167. Mono-ortho chlorine substitution for (hexa-chloro) PCB 169 yields a single compound, the hepta-chloro PCB congener 189.

For certain of the PCB congeners, there has thus been a very critical mechanistic linkage of the toxicity of certain configurations with that of the highly toxic 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and 2,3,7,8-tetrachlorodibenzofuran (TCDF). These "dioxin-like" PCB congeners are those which are co-planar (relatively flattened in shape), like TCDD/TCDF, and which contain chlorines in the non-ortho and mono-ortho positions on the molecule.

Because of this structural similarity between toxicologically significant individual PCB congeners and TCDD dioxin, theoretical health risks for the PCB congeners are assessed in a fashion similar to those for the chlorinated dibenzo-p-dioxin (CDD) and chlorinated dibenzofuran (CDF) congeners. ***That is to say, the traditional "reference dose" (RfD) approach for non cancer endpoints, is not used in assessing the various "dioxin-like" co-planar PCBs.*** Instead, the assessment of risk from these dioxin-like individual PCB congeners relies on the use of Toxicity Equivalent Factors (TEF) as described below.

Using Toxicity Equivalent Factors (TEF) as an estimate of relative toxicity**:** As mentioned elsewhere in this document, 2,3,7,8-TCDD is the most toxic and extensively studied of this general class of related compounds, and serves as a prototype for the various toxicologically relevant or "dioxin-like" PCB congeners, as well as for the various other CDD and CDF. Of all

these various related and toxicologically significant compounds, only 2,3,7,8-TCDD has thus far been assigned a oral carcinogenic slope factor (1.5E+5; which conveys the highest potency for any synthetic chemical studied thus far). Based on the results of animal studies, scientists have learned that they can express the toxicity of dioxin-like PCB congeners (and various other related CDD and CDF) as a fraction of the toxicity attributed to 2,3,7,8-TCDD. For example, the toxicity a given dioxin-like PCB congener could be half, or one tenth, or any fraction of that of

2,3,7,8-TCDD.

Scientists call that fraction a ***Toxicity Equivalent Factor (TEF)***. Although the dose necessary to elicit a toxic response differs between congeners, the relative potency of the different PCB congeners (in comparison to 2,3,7,8-TCDD) is generally consistent for each endpoint. This general consistency has allowed the World Health Organization (WHO) to develop a formal and universally accepted toxicity equivalent factor approach to convert any of the toxicologically significant co-planar PCB congeners–as well as any of the 17 possible toxicologically significant CDD/CDF congeners–into an equivalent concentration of 2,3,7,8-TCDD. Although this approach is commonly used today in the evaluation of risk due to dioxin-like co-planar PCBs, as well as for chlorinated dibenzodoxins and chlorinated dibenzofurans, it is an "interim" method, and does not necessarily replace the need for congener-specific data. (See also discussions for CDD/CDF).

Dioxin-like PCB congeners are responsible for only part of the theoretical carcinogenicity of a total PCB mixture which has been partitioned into the environmental media via natural processes over time. To account for the fact that relative concentrations of dioxin-like congeners may be enhanced in environmental mixtures, especially in fish due to bioaccumulation of the more persistent congeners, the 1998 WHO/ICPS/TEFs are used in this risk characterization process. The various TEFs assigned to each specific PCB congener are discussed below under each individual compound. (For additional background on TEFs, see also the discussion section on Dioxins/Furans)

According to Hansen (1998), the fifteen most "environmentally abundant" of the 209 various PCB congeners are: PCB 1, 3, 15, 18, 28, 31, 33, 44, 49, 52, 66, 95, 118, 153, and 180. This is of course, very debatable, and is largely dependant on the type, history, and location of the environmental media being sampled and analyzed. Prevalence in the environment is one thing; but toxicological significance is another.

PCB congeners identified at detectable levels in this report include: PCB 77, 105, 114, 118, 123, 126, 156, 157, 167, 169, 170, 180, and 189. It is important to note that all three of the (more dioxin-like) non-ortho substituted congeners, and all 6 of their possible (also toxic to some extent) mono-ortho substituted forms were detected in at least some of the fish sampled.

The chemical nature and toxicity profiles of these various individual congeners are as follow:

PCB 77: 3,3'4,4'-tetrachlorobiphenyl; CASRN 32598-13-3 (See also PCB congeners 105, 118)

Like PCB 126 and 169, PCB 77 is also a non-ortho substituted co-planar molecule, and structurally resembles TCDD and TCDF. It thus possesses significant toxicity. Because of the symmetry and positioning of the four chlorine atoms, and also because of its "co-planar structure", this PCB congener and its close relatives are structurally somewhat similar to the "dioxin" molecule (specifically, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD). Thus, the toxicity and biological significance of PCB Congener 77 and its close relatives is in general, higher than that of more highly chlorinated PCB congeners which do not share this identical chlorine configuration.

As with all the individual PCB congeners, at this time IRIS has not established a RfD for non-cancer effects for PCB 77. The available literature indicates that the oral acute toxicity of PCB 77 (guinea pig) is 1 mg/kg. In research studies of chronic exposure, at doses ranging from 7-124 mg/kg during days 10-16 of pregnancy, PCB 77 has also been shown to cause reproductive toxicity in the rat and mouse (impairment of fertility, specific developmental abnormalities, behavioral and other effects on the newborn, fetotoxicity, etc), and in the monkey (aborted fetus; 6.3 mg/kg dose given from days 20-40 of pregnancy). Additional chronic effects of PCB 77 include liver and endocrine changes (rodents), and blood and endocrine changes (monkey). PCB 77 also causes DNA adduct formation *in vitro* studies of liver from humans, rats, and quail. The WHO TEF for PCB 77 is 0.0001.

IRIS does not list an oral carcinogenic slope factor for PCB 77, or for any of the other specific PCB Congeners. However, based on various structural similarities between PCB 77 and TCDD, EPA has calculated a Relative Potency Factor of 0.0001 for PCB 77.

PCB 105: 2,3,3',4,4'-pentachlorobiphenyl; CASRN 32598-14-4

PCB 105 is a mono-ortho chlorine substituted analog of the toxic congener PCB 77. Thus, it can be likewise expected to possess significant toxicity. Because of the positioning of chlorines at the four critical ring positions, this PCB congener is thus also structurally somewhat similar to TCDD. In terms of structure-activity relationships, however, the addition of the additional chlorine at position 2 presents just enough asymmetry to "theoretically" make the molecule somewhat different in its "efficacy" at the receptor site.

Very little toxicological data could be found for this PCB congener. However, the acute intraperitoneal mouse LD50 is approximately 400 mg/kg. In mice, PCB 105 was also found to induce changes in liver, and blood. For non-cancer effects, IRIS has not at this time established a specific oral RfD for PCB 105.

IRIS has likewise at this time not established an oral carcinogenic slope factor for PCB 105. The Relative Potency Factor for PCB 105 (compared to that of TCDD) is 0.0001.

PCB 114: 2,3,4,4',5-pentachlorobiphenyl; CASRN 74472-37-0

Detailed toxicological information about PCB 114 could not be located in the available literature. As with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer effects of PCB 114.

IRIS likewise does not list an oral carcinogenic slope factor for PCB 105. However, EPA has developed a relative potency factor for this PCB congener, based on its various structural similarities to that of TCDD. For PCB 114, this relative potency factor is 0.0005.

PCB 118: 2,3',4,4',5-pentachlorobiphenyl; CASRN 31508-00-6

PCB 118 is a mono-ortho chlorine substituted analog of the toxic PCB congener 77. It can thus be expected to possess significant toxicity. PCB 118 also causes reproductive effects; most of the studies with this compound have been done with rats. Oral doses of 28-112 mg/kg during days 10-16 of pregnancy (rat) have resulted in reduced weight gain, and biochemical, metabolic, and behavioral effects on the newborn. Adult rats receiving 15 ug/kg continuously for 13 weeks have also undergone degenerative changes in brain and liver, as well as toxicant-induced changes in neurochemistry (dopamine). As with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer effects of PCB 118.

IRIS does not list an oral carcinogenic slope factor for PCB 118. However, EPA has developed a relative potency factor for this congener, based on its various structural similarities to that of TCDD. For PCB 118, this relative potency factor is 0.0001.

PCB 123: 2',3,4,4',5-pentachlorobiphenyl; CASRN 65510-44-3

Detailed toxicological information about PCB 123 could not be located in the available literature. As with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer effects of PCB 123.

IRIS does not list an oral carcinogenic slope factor for PCB 123. However, EPA has developed a relative potency factor of 0.0001 for PCB 123, based on its relative potency and structural resemblance to TCDD.

PCB 126: 3,3',4,4',5-pentachlorobiphenyl; CASRN 57465-28-8 (See also PCB congeners 156, 157, and 167)

Like PCB 77 and 169, PCB 126 is also a non-ortho substituted, coplanar molecule, which thus resembles the structure of TCDD and TCDF, and subsequently possesses significant toxicity. PCB 126 has been found to cause specific developmental abnormalities in mice. These include urogenital abnormalities (doses of 131 ug/kg, and 522 ug/kg, 10 D of pregnancy), and craniofacial abnormalities involving nose and tongue (522 and 783 ug/kg, 10D of pregnancy). Other maternal effects were noted at the higher dose. As with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer effects of PCB 126.

IRIS does not list an oral carcinogenic slope factor for PCB 126. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 126, the relative potency factor is 0.1, which is the highest TEQ developed thus far for any specific PCB congener.

PCB 156: 2,3,3',4,4',5-hexachlorobiphenyl; CASRN 38380-08-4

In terms of chlorine substitution on the biphenyl ring, PCB 156 is a mono-ortho substituted analog of the significantly toxic coplanar PCB 126. It would thus be presumed to have significant biological activity, and subsequent toxicity. In the mouse, an 80 mg/kg dose from 10-13D of pregnancy produced reproductive effects; specifically these were developmental abnormalities in the urogenital system. A dose of 480 mg/kg administered over the same time interval in pregnant dams produced craniofacial developmental abnormalities in nose and tongue. In the rat, 33.3 mg/kg continuous dose resulted in multi-organ effects, characterized by changes in the weights of liver, kidney, ureter, bladder and thymus. As is the case with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer effects of PCB 156.

IRIS does not list an oral carcinogenic slope factor for PCB 156. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 156, the relative potency factor is 0.0005.

PCB157: 2,3,3',4,4',5' hexachlorobiphenyl; CASRN 69782-90-7

In terms of chlorine substitution on the biphenyl ring, PCB 157 is a mono-ortho substituted analog of the significantly toxic congener, PCB 126. It can thus be presumed to have a significant likelihood of biological activity, and subsequent toxicity. (According to RTECS, PCB 157 is similar in health effects to PCB 156. This would seem mechanistically plausible, since both are mono-ortho substituted analogs of PCB 126. See above information for PCB 156.) As is the case with all individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer endpoints of PCB 157.

IRIS does not list an oral carcinogenic slope factor for PCB 157. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 157, the relative potency factor is 0.0005.

PCB 167: 2,3',4,4',5,5'-hexachlorobiphenyl; CASRN 52663-72-6

In terms of chlorine substitution on the biphenyl ring, PCB 167 is a mono-ortho substituted analog of the significantly toxic congener, PCB 126. It would thus be presumed to have a significant likelihood of biological activity and subsequent toxicity.

Detailed toxicological information about PCB 167 could not be located in the available literature. As is the case with all the various individual PCB Congeners, IRIS has not at this time derived an oral RfD for non-cancer endpoints of PCB 167.

In like fashion, IRIS does not list an oral carcinogenic slope factor for PCB 167. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 167, the relative potency factor is 0.00001.

PCB 169: 3,3',4,4',5,5'-hexachlorobiphenyl; CASRN 32774-16-6 (See also PCB 189)

Like PCB 77 and PCB 126, PCB 169 is a non-ortho substituted co-planar molecule, which resembles that of TCDD and TCDF, and thus possesses significant toxicity. Oral LD50 for the guinea pig (by far the most sensitive species to "dioxin-like" toxicity) is 223 ug/kg. In the mouse, reproductive toxicity studies of PCB 169 given at doses of 10 mg/kg, to pregnant females from days 6-15 resulted in developmental abnormalities in the hepatobiliary system. A dose of 20 mg/kg resulted in craniofacial and urogenital developmental abnormalities. Doses of 40 and 80 mg/kg resulted in fetotoxicity and fetal death. In the rabbit, a dose of 37.8 mg/kg to pregnant females from day 1-28 caused toxic maternal effects, as well as behavioral and other postnatal effects on the newborn rabbits.

Continuous oral dosing of mice, at 58.8 mg/kg-day for 28 days resulted in multiple hepatic effects and endocrine changes. Effects on serum composition (total protein, bilirubin, cholesterol, etc.) were also noted. As is the case with all the various individual PCB Congeners, IRIS at this time has not developed an oral RfD for non-cancer effects of PCB 169.

In like fashion, IRIS does not list an oral carcinogenic slope factor for PCB 169. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 169, the relative potency factor is 0.01.

PCB 170: 2,2',3,3',4,4',5-heptachlorobiphenyl; CASRN 35065-30-6

Detailed toxicological information about PCB 170 could not be located in the available literature. As is the case with all individual PCB Congeners, IRIS at this time has not derived an oral RfD for non-cancer endpoints for PCB 170.

In terms of assessing the likelihood of possible carcinogenic effects, IRIS/EPA have likewise not developed a carcinogenic slope factor for PCB 170. At one time, PCB 170 was included on the World Health Organization (WHO) list of various PCB congeners having relative potency factors, but has now been removed from this list. At this time, no relative potency factor is thus available for PCB 170.

PCB 180: 2,2',3,4,4',5,5'-heptachlorobiphenyl; CASRN 35065-29-3

Detailed toxicological information about PCB 180 could not be located in the available literature.

As with all individual PCB Congeners, IRIS has at this time not derived an oral RfD for non-cancer effects of PCB 180.

At one time, PCB 180 was included on the WHO list of various PCB congeners having potency factors, but it has now been removed from this list. Therefore, no relative potency factor has been developed or adopted for PCB 180.

PCB 189: 2,3,3',4,4',5,5'-heptachlorobiphenyl; CASRN 39635-31-9

In terms of its chlorine substitution on the biphenyl ring, PCB 189 is a mono-ortho analog of the (significantly toxic) PCB 169, which makes it of concern from the standpoint of likely biological activity and potential toxic effects.

Detailed toxicological information about PCB 189 could not be located in the available literature. As is the case with all the various PCB Congeners, IRIS at this time has not derived an oral RfD for non-cancer effects of PCB 189.

IRIS likewise does not list an oral carcinogenic slope factor for PCB 189. However, EPA has developed a relative potency factor for this congener, based on various aspects of its structural resemblance to TCDD. For PCB 189, the relative potency factor is 0.0001.

DIOXINS AND FURANS:

"Dioxin" is a general term referring to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and its related congeners. The toxicity of the chlorinated dibenzodioxins(CDDs) and the closely related dibenzofurans (CDFs) varies with the position and number of chlorines attached to the aromatic rings of the molecule(s) in question. Under the laws of chemistry and physics, and under industrial and environmental conditions as we know them, it is chemically possible to form a total of 75 different individual chlorinated CDDs, and a total of 135 different individual CDFs. Of these, only about seventeen individual compounds (7 CDDs and 10 CDFs) are of sufficient toxicological and environmental significance to be considered in this report. These compounds constitute the seventeen different possible species of tetra-(having 4 chlorines) through octa-(having 8 chlorines) chlorinated CDDs and CDFs which can be formed and exist in the environment. Those dioxins/furans with chlorines (and sometimes other halogens like bromine) at the 2, 3, and 7 positions on the ring are particularly toxic, with 2,3,7,8-TCDD considered to be

the most toxic and biologically significant of all the various possible chlorinated dioxin/furan congeners. Likewise, the 2,3,7-8 tetrachlorodibenzofuran (TCDF) is the most toxic of the various chlorinated dibenzofuran congeners.

The chlorinated dibenzodioxins and chlorinated dibenzofurans are not produced intentionally by industrial processes. Rather, most CDDs and CDFs are generated in very small amounts as unwanted impurities of certain products and processes which utilize chlorinated compounds. Probably the most famous example of this was the finding in the late 1960's that the production process for the widely used herbicide 2,4,5-trichlorophenoxy acetic acid (2,4,5-T) also resulted in the formation of small quantities of the extremely toxic CDD contaminant, 2,3,7,8-TCDD. Herbicide 2,4,5-T was a major ingredient in the military defoliant, "Agent Orange", which was used extensively during the Vietnam War. In the post-Vietnam era, this dioxin contaminant soon gained extreme public and scientific notoriety, and over the ensuing several decades generated a tremendous amount of research interest from the biomedical community worldwide. Other production chemicals which can generate unwanted trace amounts of 2,3,7,8-TCDD included the forestry herbicide 2,4,5-Trichlorophenoxy propionic acid (Silvex), and the industrial chemical 2,4,5-Trichlorophenol. Unwanted trace amounts of some of the higher-chlorinated CDDs, especially the hexa and octa isomers, have also associated with the production of the widely used wood preservative, Pentachlorophenol (PCP).

In the case of the chlorinated dibenzofurans, most of what we know about the health effects of CDF come from studies of accidental poisonings in Japan ("Yusho Disease") and Taiwan (Yu-Cheng Disease") in the 1960s and 1970s, where over a several month period, many people ate food cooked in PCB-contaminated rice oil, which also contained CDF. In heating the PCB-contaminated oil for cooking purposes, it is presumed that additional CDF were generated. Since the formation and contributory toxicity of CDF in such PCB mixtures was relatively unknown at that time, it was at first believed that primarily PCBs were responsible for the toxicity. (See also discussion on PCBs) Adverse health effects in the exposed populations included skin and eye irritation, severe chloracne, darkened skin color and swollen eyelids with discharge. However, these effects did not develop in some people until weeks or months after exposure. Also noted were vomiting, diarrhea, anemia, more frequent lung infections, numbness and other neurological effects, and mild changes in the liver. Children born to poisoned mothers also had acne and other skin irritations. Young children of these mothers also had some learning difficulties, but whether or not this effect was permanent has not been conclusively established. It is unknown whether these health effects were caused by CDFs alone, or by CDF and PCBs in

combination.

Small amounts of CDFs/CDDs can also enter the environment from a number of other sources. As alluded to previously, accidental fires or breakdowns involving capacitors, transformers, and other electrical equipment (e.g., fluorescent light fixtures which contain polychlorinated biphenyls (PCBs) are known to release high levels of CDFs, and to a lesser extent, CDDs, formed by thermal degradation). CDFs are also produced as unwanted compounds during the manufacture of several chlorinated chemicals and consumer products, including certain wood treatment chemicals, some metals, and paper products. When the waste water, sludge, or solids from these processes are released into waterways or soil in dump sites, the sites become contaminated with CDFs/CDDs. These unwanted contaminants also enter the environment from burning municipal and industrial waste in incinerators, as well as from leaded gasoline exhaust, and the burning of coal, wood, or oil for home heating and production of electricity. Many of the various chemicals and processes which significantly produce CDFs/CDDs in the environment are either being slowly phased out or are strictly controlled. It is currently believed that CDF/CDD emissions associated with human incineration and combustion activities are the predominant environmental source. CDFs/CDDs also arise from natural sources in the environment, produced by natural thermal processes such as forest fires and volcanos.

Because of their chlorination and specific chemical structures, most CDFs/CDDs are highly fat soluble, and difficult for the body to quickly degrade and excrete. They are thus in some ways quite similar to some of the other persistent and bioaccumulative chlorinated residues like DDT, PCB, etc. Also like PCBs and the DDT group, CDFs/CDDs can bioaccumulate in fish, and the amount of CDFs in fish, for example, can sometimes be tens of thousands times higher than the levels in the surrounding water.

The liver appears to be the primary organ for acute exposure to CDDs and CDFs, but it should be also stressed that these compounds can also have other effects on a wide variety of organ systems. Effects of acute exposure include: hepatotoxicity, weight loss, psychological alterations, suppression of the immune system and death. Chronic effects include: teratogenicity, fetotoxicity, reproductive dysfunction, immunotoxicity, and carcinogenicity. For purposes of risk assessment, it is important to note that CDFs and/or CDDs are found in the environment together with other structurally-related chlorinated chemicals, such as some of the various co-planar PCB congeners (see PCB discussion). Therefore, people are generally exposed to mixtures of these structurally similar compounds, rather than to a single CDF, CDD or PCB congener.

In terms of toxicity and risk assessment, the "reference dose" (RfD) approach (for non-cancer endpoints) is not used in assessing any of the various toxicologically significant CDD /CDF congeners. Nor is it utilized in assessing non-cancer risks from the various "dioxin-like"co-planar PCB congeners (see also PCB section).

Using Toxicity Equivalent Factors (TEF) as an estimate of relative toxicity: As mentioned previously in the discussion section for PCB congeners, 2,3,7,8-TCDD is the most toxic and extensively studied of the CDDs, and serves as a prototype for the toxicologically relevant or "dioxin-like CDD, CDF and PCB congeners. Based on results from animal studies, scientists have learned that they can express the toxicity of dioxin-like CDFs, CDDs, and co-planar PCBs as a fraction of the toxicity attributed to 2,3,7,8-TCDD. For example, the toxicity of dioxin-like CDDs can be half, or one tenth, or any fraction of that of 2,3,7,8-TCDD. Scientists call that fraction a ***"Toxicity Equivalent Factor" (TEF)***. Although the dose necessary to elicit a toxic response differs between congeners, the relative potency of the different dioxin/furan compounds (in comparison to 2,3,7,8-TCDD and 2,3,7,8-TCDF) is generally consistent for each endpoint. This general consistency has allowed the World Health Organization (WHO) to develop a formal and universally accepted toxicity equivalent factor (TEF) approach to convert any of the seventeen possible toxic CDF/CDD congeners into an equivalent concentration of 2,3,7,8-TCDD. Although this approach is commonly used today in the evaluation of risk due to chlorinated dibenzodioxins, chlorinated dibenzofurans, and "dioxin-like" co-planar PCBs, it is an "interim" method, and does not necessarily replace the need for congener-specific data. (See also discussion section for PCB congeners.)

2,3,7,8-TCDD Dioxin has a high cancer potency rating, with the highest slope factor for any synthetic organic compound thus far studied. TCDD target organs for carcinogenic tumors in animals include: liver, thyroid, lung, skin and soft tissue. As is the case with the various toxicologically significant co-planar PCBs (see also PCB section), carcinogenic slope factors have not been developed for any of the various CDFs, including the ten toxicologically significant ones discussed in this report. Of the seven different CDD congeners in this report, an oral carcinogenic slope factor has been developed only for 2,3,7,8-TCDD. The EPA has classified 2,3,7,8-TCDD as a Class B2 (probable human) carcinogen with a slope factor of 1.5E+5, based on hepatocellular carcinomas and lung tumors observed in rodents. Currently, the slope factor is being re-evaluated due to recent advances in understanding of the mechanisms of dioxin toxicity and of the carcinogenic and noncarcinogenic health effects observed epidemiologically among exposed populations. However, because the EPA has not yet issued a final revision, the existing

slope factor--1.5E+5 as currently listed on HEAST--is used for 2,3,7,8-TCDD in this evaluation.

WHO TEF values for the various individual chlorinated dibenzo-p-dioxin isomers are listed as follow:

CHLORINATED DIBENZO-P-DI0XINS (CDDs) 2,3,7,8-TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; CASRN 1746-01-6

The relative potency factor (WHO TEF) is 1.0.

1,2,3,7,8-PeCDD: 1,2,3,7,8-Pentachlorodibenzo-p-dioxin; CASRN 40321-76-4

The relative potency factor (WHO TEF) is 1.0.

1,2,3,4,7,8-HxCDD: 1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin; CASRN 39227-28-6

The relative potency factor (WHO TEF) is 0.1.

1,2,3,6,7,8-HxCDD: 1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin; CASRN 57653-85-7

The relative potency factor (WHO TEF) is 0.1.

1,2,3,7,8,9-HxCDD: 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin; CASRN 19408-74-3

The relative potency factor (WHO TEF) is 0.1.

1,2,3,4,6,7,8-HpCDD: 1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin; CASRN 35822-46-9

The relative potency factor (WHO TEF) is 0.01.

OCDD: Octachlorodibenzo-p-dioxin; CASRN 3268-87-9

The relative potency factor (WHO TEF) is 0.0001.

Dibenzofuran: CASRN 132-64-9

For noncarcinogenic effects, IRIS has listed an RfD of 4E-3 mg/kg/day. However, that RfD has been withdrawn, and is currently under further review by the EPA.

At this time, no carcinogenic slope factor has been developed for dibenzofuran.

CHLORINATED DIBENZOFURANS (CDFs):

Relative potency factors for the various individual chlorinated dibenzofuran isomers are listed as follow:

2,3,7,8-TCDF: 2,3,7,8-Tetrachlorodibenzofuran; 2,3,7,8-Tetrachlorodiphenylene oxide; CASRN 51207-31-9

The relative potency factor (WHO TEF) is 0.1.

1,2,3,7,8-PeCDF: 1,2,3,7,8-Pentachlorodibenzofuran; 1,2,3,7,8-Pentachlorodiphenylene oxide; CASRN 57117-41-6

The relative potency factor(WHO TEF) is 0.05.

2,3,4,7,8-PeCDF: 2,3,4,7,8-Pentachlorodibenzofuran; 2,3,4,7,8-Pentachlorodiphenylene oxide; CASRN 57117-31-4

The relative potency factor (WHO TEF) is 0.5.

1,2,3,4,7,8-HxCDF: 1,2,3,4,7,8-Hexachlorodibenzofuran; 1,2,3,4,7,8-Hexachlorodiphenylene oxide; CASRN 70648-26-9

The relative potency factor (WHO TEF) is 0.1.

1,2,3,6,7,8-HxCDF: 1,2,3,6,7,8-Hexachlorodibenzofuran; 1,2,3,6,7,8-Hexachlorodiphenylene oxide; CASRN 57117-44-9

The relative potency factor (WHO TEF) is 0.1.

1,2,3,7,8,9-HxCDF: 1,2,3,7,8,9-Hexachlorodibenzofuran; 1,2,3,7,8,9-Hexachlorodiphenylene oxide; CASRN 55673-89-7

The relative potency factor (WHO TEF) is 0.1.

2,3,4,6,7,8-HxCDF: 2,3,4,6,7,8-Hexachlorodibenzofuran; 2,3,4,6,7,8-Hexachlorodiphenylene oxide; CASRN 60851-34-5

The relative potency factor (WHO TEF) is 0.1.

1,2,3,4,6,7,8-HpCDF: 1,2,3,4,6,7,8-Heptachlorodibenzofuran; 1,2,3,4,6,7,8-Heptachlorodiphenylene oxide; CASRN 67562-39-4

The relative potency factor (WHO TEF) is 0.01.

1,2,3,4,7,8,9-HpCDF: 1,2,3,4,7,8,9-Heptachlorodibenzofuran; 1,2,3,4,7,8,9-Heptachlorodiphenylene oxide; CASRN 55673-89-7

The relative potency factor (WHO TEF) is 0.01.

OCDF: Octachlorodibenzofuran; 1,2,3,4,6,7,8,9-Octachlorodibenzofuran; 1,2,3,4,6,7,8,9-Octachlorodiphenylene oxide; CASRN 39001-02-0

The relative potency factor (WHO TEF) is 0.0001.

Nitrobenzene: CASRN 98-95-3

Nitrobenzene is an industrial chemical which is used in the manufacture of aniline, benzidine and quinoline. It is also used as a solvent, and in making lubricating oils, soap and shoe polish, as well as a preservative in spray paints. Because of these many uses, nitrobenzene may be released to the environment via various waste streams. The general population is most likely exposed to nitrobenzene via the inhalation of ambient air containing this compound, or by skin exposure to products and water containing it. Although photodegradation of this compound in water is relatively slow (half-life of about 133 days), nitrobenzene is expected to readily biodegrade under anaerobic conditions (50 per cent was degraded in 14 days when mixed with sewage inoculum). Nitrobenzene does not appear to biomagnify in aquatic ecosystems.

In humans, repeated exposures to high levels of nitrobenzene reacts with the red blood cells in the

body, to produce methemoglobin. This reduces the ability of the blood to carry oxygen to vital tissues, and results in such symptoms as headache, irritability, weakness, drowsiness, etc. There is also some evidence that breathing high concentrations of nitrobenzene can harm the liver and/or kidney, and that the permissible occupational exposure levels might not necessarily be fully protective in the workplace. The toxic effects on blood and liver have also been demonstrated in laboratory exposure studies with rodents. Nitrobenzene is metabolized by the body to form
p-nitrophenol and p-amino-phenol, which can be detected in the urine as a means of monitoring long-term (chronic) exposure.

The oral RfD for nitrobenzene is 5E-4mg/kg/day. This is based on a subchronic (90 day) rat/mouse inhalation study, with critical toxicological endpoints which include hematologic, adrenal, renal and hepatic lesions. The LOAEL (mice) for this study was 4.6 mg/kg/day (as converted from 25 mg/m3). For this RfD, the uncertainty factor is very high; 10000. This represents two 10-fold factors for both intra and inter-species variability, a 10-fold factor for estimating a chronic effects level from its subchronic equivalent, and an additional 10-fold factor for estimating an RfD from a LOAEL rather than from a NOAEL. Confidence in the RfD is thus low.

In terms of carcinogenic evaluation, EPA has assigned a weight-of-evidence-classification for nitrobenzene, of Group D (not classifiable as to human carcinogenicity). This chemical is not anticipated to be a carcinogen.

1,2-Dichlorobenzene: Ortho-dichlorobenzene; CASRN 95-50-1

1,2-Dichlorobenzene is used as an industrial solvent, and in the manufacture of 3,4-dichloroaniline. It has also been utilized as an insecticide. When benzene is chlorinated at various positions in its six-sided ring structure, it becomes more persistent in the environment. A general tendency is the more chlorines, the greater the persistence. Although not nearly as bioaccumulative and environmentally persistent as DDT or PCBs, etc, the potential for bioconcentration of this chemical in aquatic organisms is considered moderate to high, based on bioconcentration factors (BCF) in the range of 90 to 560, as measured in fish. Not surprisingly, 1,2-dichlorobenzene has thus been detected at low levels in a wide range of environmental samples. These have included various species of great lakes fish in the 1980s (1 ppb or less), flatfish off Los Angeles (up to 4 ppb), various European fish samples, etc. It has also been

detected in human milk and adipose tissue.

Acute exposure to high doses of 1,2-dichlorobenzene primarily causes injury to liver. A secondary target organ is the kidney. Short exposures to high concentrations may also depress the central nervous system. NIOSH indicates that individuals who have pre-existing liver, kidney, skin, or chronic respiratory disease are at increased risk of adverse health effects if they are exposed to this chemical.

The oral RfD for 1,2-dichlorobenzene is 9E-2 mg/kg/day, based on a 2-year oral exposure study in rats. No critical toxicological endpoint was identified. NOAEL for this study was set at 120 mg/kg/day, adjusted to 85.7 mg/kg/day. An uncertainty factor of 1000 was applied, based on a 10-fold factor to account for uncertainty in extrapolating dose levels from laboratory animals to humans, another 10-fold factor for uncertainty in the threshold for sensitive humans, and a third 10-fold factor to account for the uncertainty due to the lack of studies assessing reproductive effects and other endpoints which were not adequately explored in the study design. Confidence in the RfD is low.

In terms of evaluating this chemical for likelihood of carcinogenicity, EPA has placed 1,2-dichlorobenze in Group D (not classifiable as to human carcinogenicity). This is based on no human data, and on rodent data which are quite equivocal, showing both positive and negative trends.

1,3-Dichlorobenzene: meta-dichlorobenzene; CASRN 541-73-1

1,3-dichlorobenzene has been produced industrially for use in fumigation. It has also been marketed and applied as an insecticide. The chlorination of benzene tends to increase its environmental persistence. In general, the greater the chlorination, the greater the persistence. Thus–although not nearly as bioaccumulative and persistent in the environment as DDT and PCBs-1,3-dichlorobenzene has been detected frequently in a wide range of environmental samples and media. According to the TOXNET database, a zero per cent theoretical BOD in sludge for this compound, over a 4 week incubation period suggested that biodegradation is expected to be slow in soil and water. A survey of human milk from the Canadian general population, detected 1,3-dichlorobenzene residues in 17 per cent of the samples, at an average concentration of 2 parts per billion (ppb).

Like other dichlorobenzenes, the primary target organ for 1,3-dichlorobenzene is the liver, where it is metabolized the mixed-phase microsomal oxidizing enzyme systems. A secondary toxic endpoint is the kidney.

NCEA has derived a provisional oral RfD of 9E-4 mg/kg/day, for 1,3-dichlorobenzene. This is based on a 1995 oral subchronic toxicity study in rats. Specific toxic endpoints involved thyroid and liver. At the test dose (9 mg/kg/day), significant increases in the incidence of colloid density depletion in the thyroid follicles, increases in serum cholesterol and SGOT levels, and decreases in serum LDH levels were noted over the 90 day dosing period. At higher doses, liver and anterior pituitary gland effects and possible hypermetabolism were observed. This study did not identify a NOAEL. The provisional RfD was obtained by dividing the LOAEL of 9 mg/kg/day by an uncertainty factor of 10,000. This was necessary to account for the uncertainty associated with extrapolating frm a LOAEL identified in a subchronic study, interspecies extrapolation, human variability, and limitations in the database, especially the lack of toxicity data in a second species and the lack of adequate developmental and reproductive toxicity studies. Confidence in the provisional RfD is low.

At this time, EPA has not assessed this chemical in terms of potential carcinogenicity.

1,4-Dichlorobenzene: para-dichlorobenzene; CASRN 106-46-7

1,4-dichlorobenzene does not occur naturally. It has been produced and used extensively as an insecticide and deodorant. It is also used in making resins. It is one of the two chemicals (the other being naphthalene, which is more toxic, and has been largely phased out in favor of 1,4-dichlorobenzene) used commonly to make mothballs. It is also in making deodorant blocks for restrooms and garbage cans, and in controlling animal odors in stalls and similar confined areas. It is also used as an insecticide on fruit and a mildicide on tobacco, leather and some fabrics. Some toilet bowl cleaners also contain this chemical.

Because of such widespread use in our daily lives, 1,4-dichlorobenzene has been detected in the environment quite frequently. Somewhat not surprisingly for example, it has been found in about 13 per cent of the drinking water samples which utilize surface water sources. The average daily adult intake of this chemical is estimated by ATSDR to be about 35 micrograms, which comes primarily from breathing vapors of 1,4-dichlorobenzene that are released from products in the home. Although it, like the other chlorobenzenes, does possess some toxicity at sufficient levels

of dose, these levels encountered in our daily environmental routine are not expected to result in harmful effects. 1,4-dichlorobenzene has been detected in fish; levels of about 1 to 4 parts per billion have been measured in trout taken from the Great Lakes.

In humans, airborne concentrations of 1,4-dichlorobenzene in excess of 160 ppm are usually intolerable. However, under continuous levels of high workplace exposure, accommodation can apparently occur in which high levels can become more easily tolerated by exposed individuals.

1,4-dichlorobenzene is metabolized in the body to 2,5-dichlorophenol, which-measured in the urine-can serve as an indicator of exposure.

As with other chlorobenzenes as a group, the primary toxicological endpoint after acute dosages is the liver. Sufficiently high or sustained unusual dosage can also cause hematological and neurological effects. High oral doses cause kidney damage in male rats; this is most likely mediated mechanistically by interactions with alpha-2-microglobulin, which appears to be a metabolic hallmark specific to this gender and species. At very high inhaled concentrations, 1,4-dichlorobenzene is also irritating to the lung.

In an assessment of chronic toxicity and allowable risk, at low levels of exposure, NCEA has derived a provisional RfD of 3E-2 mg/kg/day, for 1,4-dichlorobenzene. This based on a 1994 two-generation subchronic rat fertility study. The critical toxic endpoints in this study were liver changes and effects on developmental toxicity. NOAEL from this study was 30 mg/kg/day. An uncertainty factor of 1000 is applied (10 each to account for interspecies extrapolation, the production of sensitive humans, and for extrapolation from subchronic to chronic effects.

At this time, EPA has not assessed this chemical in terms of likely or potential carcinogenicity.

1,2,4-Trichlorobenzene: CASRN 120-82-1

1,2,4-trichlorobenzene is produced as a solvent, organic intermediate, insecticide, and dye carrier. It is also used as a dielectric fluid, to partially replace (the much more environmentally persistent and toxicologically significant) PCBs. It this enters the environment via a number of waste stream pathways. The chlorination of benzene renders it more difficult to degrade, and thus more environmentally persistent than the parent molecule. In general, the greater the degree of chlorination, the greater the persistence. For this reason, 1,2,4-trichlorobenzene–while not nearly

as persistent or bioaccumulative as DDT and PCBs–has been frequently detected in a wide range of environmental samples. The TOXNET database indicates that for this chemical, bioconcentration factors (BCF) values in the range of 120 to 1300 measured in fish, suggest that bioconcentration in aquatic organisms is likely to be high. It can be stored in adipose tissue, and while mobilization/excretion tends to be considerably more rapid than for DDT or PCBs, this accumulation in lipid can still be significant under conditions of sufficient chronic exposure. The general population may be exposed to 1,2,4-trichlorobenzene via inhalation of ambient air, and ingestion of food and drinking water.

Like other chlorinated benzenes, sufficient doses of 1,2,4-trichlorobenzene preferentially target the liver, and kidney. As in the case of most other chlorinated organic compounds of this variety, it has been shown to induce mixed-function hepatic microsomal enzymes, as part of its biodegradation process. Apparently the metabolism of 1,2,4-trichlorobenzene is variable and complex, depending on the species. Rodent, dogs, and primates do not uniformly appear to metabolize this compound in the same fashion, according to the TOXNET databases.

The oral RfD for this chemical is 1E-2 mg/kg/day, based on a multi-generation rat reproductive study. Critical toxicological endpoints included increased adrenal weights, accompanied by vacuolization and other cellular changes. NOAEL was 14.8 mg/kg/day, with a LOAEL of 53.6 mg/kg/day. The RfD has an uncertainty factor of 1000. This reflects three 10-fold factors to respectively allow for extrapolating dose from animals to humans, allowing for sensitive humans, and to account for a lack of chronic studies. Confidence in the RfD is medium.

In terms of evaluation of this chemical for likelihood of carcinogenicity, EPA has placed this chemical in Group D (not classifiable as to human carcinogenicity).

1,2-Diphenylhydrazine: 1,1'-hydrazobis-benzene; CASRN 122-66-7

1,2-Diphenylhydrazine is a man-made chemical used the production of chemical dyes and certain medicines. Manufacture and use of diphenylhydrazine dyes is no longer practiced in the US.

Diphenylhydrazine has a low volatility and a tendency to partition into organic matrices. As such, this chemical can adhere to soil, and can be carried into the air along with windblown dust. According to ATSDR, it is rather labile in the environment. Diphenylhydrazine is rapidly transformed in water and air into various breakdown products, including azobenzene and

benzidine. It is thus not commonly found as a pollutant in food, air, or natural soils. Levels which do occur at concentrations above the range of a part per million are thus probably the result of very recent contamination. There is no commonly accepted method for monitoring exposure to diphenylhydrazine as a result of oral ingestion.

There is relatively little information available in the literature about the toxicity of diphenylhydrazine. Studies in animals indicate that diphenylhydrazine is absorbed across the GI tract after ingestion, but the percentage of the dose that is absorbed has not been quantified. The distribution and elimination of diphenylhydrazine from the body are also not well understood. The compound is metabolized to a number of breakdown products in laboratory animals including aniline, benzidine and various benzene derivatives such as aminophenols. Each of these breakdown products may have their own particular toxicity. One study (NCI, 1978) found that diphenylhydrazine produced liver and GI degeneration in rats. However, the doses in this study which elicited toxicity were fairly high; 390 mg/kg/day. Diphenylhydrazine was not shown to be a specific developmental or reproductive toxicant, however the number of studies which have looked at these endpoints are very limited.

There is currently no oral RfD for diphenylhydrazine. The dose levels observed to lead to non-cancer effects appear to be higher than those used in studies of carcinogenicity. In rodents, acute oral lethality of 1,2-diphenylhydrazine is approximately 1000 mg/kg/day, and toxic sequelae include liver damage, stomach damage, and death. Chronic oral dosing of rats in the laboratory at 40 ppm for 78 weeks have identified inflammation of lungs as a toxic endpoint. In studies of shorter duration (4 weeks) doses of 64 mg/kg/day have proven lethal. In mice, liver damage is also noted (at 400 ppm dose levels).

In terms of carcinogenic potential, EPA has classified 1,2-Diphenylhydrazine in Group B2 (possible human carcinogen). This is based on positive studies in both rats and mice. From the various available animal data, EPA has calculated an oral carcinogenic slope factor of 8.0E-1 mg/kg/day-1, for 1,2-Diphenylhydrazine. The slope factor is based on a National Cancer Institute (NCI) study (1978) in which rats and mice were fed diphenylhydrazine for 78 weeks. Increases in liver tumors (hepatocellular carcinomas and neoplastic nodules) were observed in treated male and female rats and treated female mice, but not in treated male mice. Female rats also developed breast tumors and male rats developed some skin cancers.

References

1. ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Toxicological Profile for 1,2-diphenylhydrazine TP-91/26
2. NCI (National Cancer Institute.) 1978. Bioassay of Hydrazobenzene for Possible Carcinogenicity. U.S. DHEW Publication No. (NIH) 78-1342.

2,4-Dinitrotoluene: (2,4-DNT); 1-Methyl-2,4-dinitrobenzene; CASRN 121-14-2

2,4-dinitrotoluene is produced and used in the manufacture of dyes, ammunition, plasticizers in propellants, and in the manufacture of toluene diisocyanate. Available information suggests that this material is not widespread in the environment. The main group of persons at high risk for exposure to 2,4-dinitrotoluene is industrial workers involved in the manufacture or handling of this material in facilities such as ammunition, dye, and polyurethane plants. Potential for bioaccumulation in aquatic organisms is low.

Exposure to high doses of this material in animals has caused decreased sperm count, and reduced fertility. Animal studies have also shown that nervous system disorders, liver damage, and kidney damage can occur, as well as a reduction in the numbers of red blood cells.

The oral RfD for this chemical is 2E-3 mg/kg/day, based on a two-year feeding study in dogs. Critical toxic endpoint was neurotoxicity, with some hematologic and biliary tract effects also noted. This RfD has an uncertainty factor of 100, to account for inter and intra-species variability. Confidence in the RfD is high.

Evaluated singly, 2,4-dinitrotoluene has not undergone a complete assessment by EPA in terms of possible carcinogenicity, nor has a carcinogenic slope factor been derived.

NOTE: EPA has evaluated "dinitrotoluene mixture", which contains both 2,4-dinitrotoluene, and 2,6-dinitrotoluene. It has assigned this mixture a carcinogenicity weight-of-evidence classification of B2 (probable human carcinogen), based on findings of multiple benign and malignant tumor types at multiple sites in both sexes of rats (2 strains), and malignant renal tumors in male mice. This classification is also supported by mutagenic evidence.

2,6-Dinitrotoluene: (2,6-DNT); 1-Methyl-2,6-dinitrobenzene; CASRN 606-20-2

The oral RfD for 2,6-dinitrotoluene is 1E-3 mg/kg/day. HEAST lists an uncertainty factor of 3000. Critical toxicologic endpoints in the rodent were mortality, Heinz body formation (seen in red blood cells; indicates abnormal hemoglobin), neurotoxicity, methemoglobinemia, bile duct hyperplasia and kidney histopathologies.

Evaluated singly, 2,6-dinitrotoluene has not undergone a complete assessment by EPA in terms of possible carcinogenicity, nor has a carcinogenic slope factor been derived.

NOTE: EPA has evaluated "dinitrotoluene mixture", which contains both 2,4-dinitrotoluene and 2,6-dinitrotoluene. It has assigned this mixture a carcinogenicity weight-of-evidence classification of B2 (probable human carcinogen), based on findings of multiple benign and malignant tumor types at multiple sites in both sexes of rats (2 strains), and malignant tumors in male mice. This classification is also supported by mutagenic evidence.

POLYCYCLIC AROMATIC HYDROCARBONS (PAH):

The PAHs consist of a group of more than 100 different compounds, all of which have three or more hydrocarbon rings as part of their structure. Among this large group of PAHs, a core group of about twenty are frequently noted as common environmental contaminants. Some of these more environmentally common PAHs and their respective CASRN numbers include:

Acenapthene: 83-29-9
Acenapthylene: 208-96-8
Anthracene: 120-12-7
Benz[a]anthracene: 56-55-3
Benzo[a]pyrene: 50-32-8
Benzo[e]pyrene: 192-97-2
Benzo[b]fluoranthene: 205-99-2
Benzo[k]fluoranthene: 207-08-9
Benzo [g,h,i] perylene: 91-24-2
Benzo[j]fluoranthene: 205-82
Chrysene: 218-01-9
Dibenz[a,h] anthracene: 3-70-3
Fluoranthene: 206-44-0
Fluorene: 86-73-7
Indeno[1,2,3-c,d]pyrene: 193-39-5
Phenanthrene: 85-01-8
Pyrene: 129-00-00

PAHs are common constituents of the environment, produced primarily by the burning of carbon-based materials, such as coal, oil and gas, garbage, etc. Other environmental input of PAHs comes from natural sources such as volcanoes, as well as from human sources such as automotive exhaust, power plant emissions or wood burning fireplaces. PAHs are found in the human diet, being particularly elevated in barbequed meats. PAHs are also present in tobacco smoke. Most PAHs have no significant industrial uses but are present in a number of commercial products including asphalt, roofing tar and creosote. A few are used in medicines, or to make dyes, plastics, and pesticides. Compared to chlorinated organics like DDT and PCBs, PAH are not so extremely persistent and/or bioaccumulative, in the general sense. However, depending on the type(s) and quantities of PAH involved, as well as the environmental medium in question (e.g., sediment), and the conditions at hand, PAH contamination can sometimes persist for a quite significant amount of time. PAHs generally have limited solubility in water so they are likely to be present at higher concentrations in soil or sediment than in water. PAHs have very low vapor pressures but may be present in air in particulate form, particularly in the vicinity of fires or fuel exhausts. There is no commonly available method for determining whether you have been exposed to PAHs.

Considerable effort has been devoted to studying the toxicological effects of PAHs. Studies in

both humans and animals indicate that PAHs are absorbed across the GI tract and across the skin. Studies in rats have indicated that the GI absorption of PAHs is likely to be less than 100%, though the actual amount absorbed will depend on the specific PAH involved and the presence of other materials in the GI tract. Similar factors govern the degree of dermal absorption. Once absorbed, PAHs are found principally in the liver, kidneys and fat (ATSDR, 1995). PAHs are eliminated from the body after metabolism to more water soluble compounds. For any given PAH, the major endpoint of such biotransformation is to form detoxified metabolites which are rapidly excreted from the body. Studies in rats have indicated that much of the absorbed dose of PAHs is eliminated within several days after exposure (ATSDR, 1995).

Non-cancer Health Risks: Oral exposure to PAHs has been reported to cause increases in relative liver and kidney weight and some alterations in blood composition in laboratory animals (ATSDR, 1995). Mild pathological effects have also been observed in the kidney with certain PAHs (i.e., fluoranthene, pyrene). Exposure of mice to one PAH, benzo(a)pyrene, at a dose of 40 mg/kg/day during pregnancy did result in reduced pup weights and pup survival, as well as reproductive dysfunction in the progeny. Developmental effects of other PAHs have not been well characterized.

Oral RfDs have been established for a small number of environmentally important PAHs, primarily those which have not been demonstrated to be carcinogenic. These RfDs and the effect(s) on which they are based are discussed in greater detail under the toxicological profiles for each individual PAH compound (see below).

Carcinogenesis: Certain PAHs (benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene and indeno[1,2,3-c,d]pyrene) have been found to cause cancer in laboratory animals by both the oral and dermal routes of exposure. No studies have indicated that PAHs cause cancer in humans after ingestion, but studies of workers exposed to mixtures of PAHs in air have shown an increased cancer incidence (ASTDR, 1995). The ability these PAHs to cause cancer depends on metabolism of the PAH to form a reactive intermediate which may damage DNA. PAHs such as acenapthene, acenapthylene, anthracene, fluoranthene, fluorene, phenanthrene and pyrene have not been demonstrated to be carcinogenic; however, the available chronic data for these compounds is somewhat limited.

As stated above, certain PAHs have been demonstrated to cause cancer in laboratory animals. As part of PAH mixtures, they have also been shown to cause cancer in humans (IRIS, 2000). To

characterize the carcinogenic potency of these PAHs, EPA has developed a relative potency approach. Because the carcinogenic properties of benzo[a]pyrene have been studied most extensively, EPA (1993) has developed a cancer potency factor for this compound and related the carcinogenic potency of the other compounds to that of benzo[a]pyrene. The corresponding cancer values are as follows:

	Relative Potency Factor
Benzo[a]pyrene	1.0
Benz[a]anthracene	0.1
Benzo[b]fluoranthene	0.1
Benzo[k]fluoranthene	0.01
Chrysene	0.001
Dibenz[a,h]anthracene	1.0
Indeno[1,2,3-cd]pyrene	0.1

References

1. ATSDR (Agency for Toxic Substances and Disease Registry. 1995. Toxicological Profile for Polycyclic Aromatic Hydrocarbons (Update). US Dept. of Health and Human Services. Atlanta, GA

2. EPA, 1993. Provisional guidance for quantitative risk assessment of polycyclic aromatic hydrocarbons. Environmental Criteria and Assessment Office. Cincinnati, OH. Final Draft. ECAO-CIN-842.

3. IRIS (Integrated Risk Information System). 2000. EPA on-line database.

Acenaphthene: 1,2-Dihydroacenapthylene; CASRN 83-29-9

Like other PAH, acenaphthene entering the environment is rarely found singly in a given waste stream, but is normally part of a complex mixture containing other PAH, along with many other associated compounds. As with other PAH, acute toxicity from acenaphthene is rarely reported. It does undergo microbial degradation, and is readily metabolized by multicellular organisms. EPA indicates that the half-life of acenaphthene in bluegill sunfish is less than one day.

The oral RfD for acenaphthene is 6E-2 mg/kg/day, based on a mouse oral subchronic study. Critical effect was hepatotoxicity, as evidenced by increased liver weights and enzyme changes. NOAEL for the study was 175 mg/kg/day, with a LOAEL of 350 mg/kg/day. EPA IRIS lists an uncertainty factor of 3000, and confidence in the oral RFD is low.

Acenaphthene has not been evaluated by EPA for carcinogenic potential at this time.

Acenaphthylene: Cyclopenta[d,e]naphthalene; CASRN 208-96-8

As with other PAH, acute toxicity from exposure to acenaphthene is rarely reported. The most likely exposure to acenaphthylene and other PAH is probably occupational, in places associated with processing, manufacture or use of materials like fossil fuels, coal tar, asphalt, carbon black, etc. Non-occupational exposures would most likely take place via urban atmospheres, contaminated drinking water supplies and recreational activities at contaminated sites.

Acenephthylene at this time has no RfD listed on IRIS.

In terms of carcinogenic potential for this PAH, IRIS has classified it in Group D (not classifiable as to human carcinogenicity). This is because of a lack of available human data, and inadequate data from animal bioassays.

Anthracene: Paranaphthalene; CASRN 120-12-7

As with other PAH, acute toxicity from anthracene is relatively rare. The oral RfD for anthracene is 3E-1 mg/kg/day, based on a 1989 EPA study of subchronic toxicity in mice. No treatment-related, specific toxicologic endpoints were noted in the mice at the doses administered. Accordingly, the NOAEL was assumed to be 1000 mg/kg/day, which was the highest dose tested. IRIS has assigned an uncertainty factor of 3000 for this RfD, and confidence in the RfD is likewise low. No LOAEL dose was derived.

In terms of carcinogenic potential, anthracene is classified by EPA IRIS in Group D (not classifiable as to human carcinogenicity). This is due to lack of adequate data on this PAH.

Benz[a]anthracene: Benzo[b]phenanthrene; CASRN 56-55-3

As with other PAH, acute toxicity from benz[a]anthracene is rarely reported. No oral RfD has been developed for this PAH, at this time.

In terms of its likely carcinogenic potential, EPA has placed benz[a]anthracene in Group B2 (probable human carcinogen). No oral carcinogenic slope factor has been developed for this PAH. However, EPA has established a relative carcinogenic potency factor of 0.1 for this PAH, based on the carcinogenic slope factor for benzo[a]pyrene.

Benzo[a]pyrene (BaP): Benzo[d,e,f]chrysene; CASRN 50-32-8

As with other PAH, acute toxicity from this compound is rarely noted. At this time, no oral RfD has been developed for this PAH.

In terms of its likely carcinogenic potential, EPA has placed BaP in Group B2 (probable human carcinogen). Although human data lacking BaP to a specific carcinogenic effect are lacking, the carcinogenicity of this compound in animal studies is extremely well documented, in numerous species, and by numerous dosing routes. The various animal data include dietary, gavage, inhalation, intratracheal instillation, dermal and subcutaneous studies in numerous strains of at least four species of rodents and several primates. Repeated BaP administration has been associated with increased incidences of total tumors, as well as tumors at the site of exposure. Distant site tumors have also been observed after BaP administration by various routes. BaP is frequently used as a positive control in carcinogenicity bioassays.

The oral carcinogenic slope factor for Benzo[a]pyrene is 7.3E+0 mg/kg/day. The relative carcinogenic potency factor for benzo[a]pyrene, established by EPA, is 1.0. Benzo[a]pyrene is the "standard" upon which the theoretical cancer potencies of the various other PAH compounds are modeled.

Benzo[b]fluoranthene: 3,4-Benz[e]acephenanthrylene; CASRN 205-99-2

As with other PAH, acute toxicity is rarely noted. At this time, no oral RfD has been developed for this PAH.

In terms of its likely carcinogenic potential, EPA has placed this PAH in Group B2 (possible human carcinogen). Although human data are lacking, this PAH has been found to produce

tumors in mice via several dosage routes–including lung implantation, injection, and direct application to skin.

EPA has established a relative potency factor of 0.1, for this PAH. This is based on comparisons to the relative potency of BaP, which serves as the standard for developing such PAH cancer potency models.

Benzo[k]fluoranthene: 8.9-Benzfluoranthene; CASRN 207-08-9

Like all PAH, acute toxicity from benzo[k]fluoranthene is infrequently noted. At this time, no oral RfD has been developed for this PAH.

In terms of its likely carcinogenic potential, EPA has placed this PAH in Group B2 (possible human carcinogen). Although human data are lacking, this PAH has produced tumors when administered as a promoting agent in skin painting studies with mice. It has also produced tumors after implantation in the mouse lung, and is known to be mutagenic in bacteria.

EPA has established a relative potency factor of 0.01 for this PAH, as based on its relationship to the carcinogenic potency of the BaP standard.

Chrysene: 1.2-Benzophenanthrene; CASRN 218-01-9

At this time, no oral RfD has been established for Chrysene.

In terms of likely carcinogenic activity, EPA has placed chrysene in Group B2 (probable human carcinogen).

EPA has established a relative potency factor of 0.001 for this PAH, in comparison to the carcinogenic potency of BaP.

Dibenz[a,h]anthracene: ,2:5,6-Dibenz[a]anthracene; CASRN 53-70-3

At this time, nor oral RfD has been established for Dibenz[a,h]anthracene.

In terms of likely carcinogenic potential, EPA has placed this PAH in Group B2 (probable human carcinogen).

EPA has established a relative potency factor of 1.0 for dibenz[a,h,]anthracene, which makes it equipotent in this sense to (the classic and thoroughly studied, prototypical PAH carcinogen), BaP. Dibenz[a,h]anthracene produced carcinomas in mice after oral or dermal exposure, as well as injection site tumors in several species after intramuscular or subcutaneous administration. It has also induced gene mutations and DNA damage in bacteria, and gene mutations and transformation in several types of mammalian cell cultures.

Fluoranthene: 1.2-[1,8-Naphthylene]benzene; CASRN 206-44-0

The oral RfD for fluoranthene is 4E-2 mg/kg/day, based on a mouse subchronic study. Target toxicity endpoints included kidney damage, increased liver weights, hematological alterations and clinical effects. NOAEL was 125 mg/kg/day, with a LOAEL of 250 mg/kg/day. With an uncertainty factor of 3000, IRIS notes that the confidence in the RfD is low.

At this time, no cancer potency factor has been developed for fluoranthene. Due to lack of data, EPA has designated this PAH as Group D (not classifiable as to carcinogenicity).

Fluorene: Ortho-biphenylene methane; CASRN 86-73-7

The oral RfD for fluorene is 4E-2 mg/kg/day, based on a 1989 mouse subchronic study, which revealed critical hematological toxic endpoints of decreased red blood cells, packed cell volume, and hemoglobin. An uncertainty factor of 3000 is applied to this RfD. Confidence in the RfD is accordingly low.

At this time, no cancer potency factor has been developed for fluorene. Due to lack of data, EPA has designated this PAH as Group D (not classifiable as to carcinogenicity).

Indeno(1,2,,3-cd)pyrene: 1,10-[1,2-Phenylene]pyrene; CASRN 193-39-5

At this time, no RfD has been developed for this PAH.

EPA has classified this PAH in Group B2 (possible human carcinogen).

EPA has established a relative potency factor of 0.1 for this PAH, as compared to the standard potency (1.0) for BaP.

Pyrene: benzo[d,e,f]phenanthrene; CASRN 129-00-00

The oral RfD for pyrene is listed in IRIS, at 3E-2 mg/kg/day. This is based on an oral mouse subchronic bioassay, with critical effects manifesting as kidney toxicity. Renal tubule pathology and decreased kidney weights were noted, with a NOAEL of 75 mg/kg/day, and a LOAEL of 125 mg/kg/day. Uncertainty factor is 3000, and confidence in the RfD is therefore low.

As for potential carcinogenicity of pyrene, EPA has assigned this PAH to Group D (not classifiable as to human carcinogenicity). No carcinogenic slope factor has been developed for pyrene.

Phenanthrene: CASRN 85-01-8

At this time, no oral RfD has been developed for phenanthrene.

In terms of likelihood for this PAH to be carcinogenic, EPA has classified phenanthrene as Group D (not classifiable as to human carcinogenicity), due to lack of adequate human and animal data.

Benzo(g,h,i)perylene: 1,12-benzoperylene; CASRN 191-24-2

At this time, no oral RfD has been developed for this PAH.

As for carcinogenic potential of this compound, EPA has placed it in Group D (not classifiable as to human carcinogenicity). This is due to lack of adequate human and animal data. No relative potency factor has been developed for this PAH.

NAPHTHALENES:

Naphthalene: CASRN 91-20-3

Naphthalene is also known as "tar camphor", and is found naturally in fossil fuels. It is also produced from burning wood, or tobacco. The major industrial products made from naphthalene are moth repellants ("moth balls"). (Most modern mothball and deodorant preparations now contain p-dichlorobenzene, which has replaced the more-toxic naphthalene. However, "old-fashioned" preparations may still contain naphthalene). Naphthalene is also used in the manufacture of resins, dyes, leather, tanning agents, and the commonly used carbamate insecticide, carbaryl.

Naphthalene does not typically bioaccumulate in the tissues of animals or fish, but it can remain in the body for as long as several weeks before it is completely broken down (mainly by the liver) and excreted. Naphthalene has an extensive number of metabolites–more than 30 have been identified in the rat and mouse. It is excreted primarily via the urine, but may also be found in the stool, as well as in breast milk after significant exposures.

Acute exposures to large amounts of naphthalene may result in hemolytic anemia, in which red blood cells are destroyed/damaged. This has been observed in humans, especially children, after ingestion of naphthalene-containing mothballs or deodorant blocks. Anemia has also occurred in infants wearing diapers after storage in mothballs. Persons who are deficient in glucose-6-phosphate dehydrogenase activity, are at increased risk for developing hemolytic anemia from acute exposure to naphthalene.

In rodents and other laboratory animals, cataract formation has been long noted to occur after exposure to large acute doses of naphthalene. Evidence from rats and rabbits suggests that this ocular toxicity is due to the formation of a liver metabolite, 1,2-dihydroxy naphthalene, which is then enzymatically converted in the eye to 1,2-napthoquinone which then reacts with eye proteins, causing the damage. In animal studies, another well-known target tissue for the effects of high doses of naphthalene is the lung; specifically the nonciliated bronchiolar epithelial cells ("Clara cells").

The oral RfD for naphthalene is 2E-2 mg/kg/day, based on a 1980 subchronic oral rat study, with a critical toxic endpoint of decreased mean terminal body weight in males. NOAEL for the study

was 100 mg/kg/day (which--because the study was a subchronic one rather than a full chronic study–was subsequently duration-adjusted to 71 mg/kg/day). LOAEL was 200 mg/kg/day, which was likewise duration-adjusted to 142 mg/kg/day. An uncertainty factor of 3000 is used in calculating the RfD, which represents separate uncertainty factors of 10 for extrapolation to humans from rats, 10 to protect sensitive human populations, 10 to extrapolate from subchronic to chronic exposure, and 3 for database deficiencies including the lack of chronic oral exposure studies and 2-generation reproductive toxicity studies. Confidence in the RfD is low.

As for likelihood of carcinogenicity, EPA has classified naphthalene in Group D (not classifiable as to human carcinogenicity), because of the lack of adequate human and animal data.

However, in February 2001, the National Toxicology Program (NTP) has completed and published a 2-year rodent inhalation of naphthalene. Results of this inhalation study show clear evidence of carcinogenic activity. At this time, however, EPA has not reviewed this information as part of its IRIS carcinogenis assessment process for this compound.

Methyl-naphthalene: 1- Alpnhalation ha-methylnaphthalene; CASRN 90-12-0

1-methylnaphthalene is utilized in the manufacture of dyes, resins and other chemicals. Along with naphthalene and 2-methylnaphthalene, it is also present in materials like wood and cigarette smoke, tar, asphalt, and some hazardous waste At this time, no RfD has been established for 1-methyl-naphthalene.

Likewise, EPA has not evaluated this compound in terms of likely carcinogenic potential.

2-Methyl-naphthalene: Beta-methylnaphthalene; CASRN 91-57-6

The uses and occurrence of 2-methylnaphthalene are similar to those reported for 1-methylnaphthalene above. In addition, 2-methylnaphthalene is also used in the production of Vitamin K.

At this time, no RfD has been established for 2-methyl-naphthalene.

Likewise, EPA has not evaluated this compound in terms of likely carcinogenic potential.

2-Chloronaphthalene: Beta-chloronaphthalene; CASRN 91-58-7

The oral RfD for 2-Chloronaphthalene is 8E-2 mg/kg/day. This is based on a mouse subchronic oral gavage study, with liver enlargement, abnormal appearance, and dyspnea as critical toxic effects. NOAEL from these data was 250 mg/kg/day, with a LOAEL of 600 mg/kg/day. The uncertainty factor for the RfD is 3000, which reflects factors of 10 each for inter- and intraspecies conversion, 10 for the use of a subchronic study to derive the chronic RfD, and 3 to account for the lack of reproductive /developmental and chronic toxicity data. Confidence in the RfD is thus low.

At this time, EPA has not evaluated 2-chloronaphthalene for likelihood of carcinogenic potential.

METALS:

Aluminum: CASRN 7429-90-5.

Aluminum is a widely distributed component of the earth's crust and is frequently found in the environment. Aluminum may enter the environment either though natural processes or human activity, such as coal combustion or aluminum mining or smelting (ATSDR, 1997). Aluminum metal is widely used in such products as cooking utensils, machine parts, food and beverage containers and structural components of buildings and aircraft. Aluminum alloys and compounds are also used in products such as antacids, deodorants, dental materials, and drinking water additives. Due to the ubiquitous nature of aluminum in the environment, aluminum is also found in food and drinking water. The typical dietary intake of aluminum from food and drinking water is approximately 10 mg/day. Aluminum does not appear to be an essential dietary element. Exposure to aluminum may be assessed through urinary measurements.

Absorption of aluminum across the GI tract appears to be fairly low, perhaps less than 1 percent (ATSDR, 1997). However, the degree to which aluminum is absorbed will depend on material with which it was ingested and the nutrient status of the individual. Once absorbed, aluminum is distributed throughout the body with about half the body burden found in the skeleton (ATSDR, 1997). Excess aluminum is eliminated rapidly from the body, with most of the absorbed dose eliminated in the urine (ATSDR, 1997).

Aluminum toxicity after oral exposure has not been conclusively observed in humans (ATSDR, 1997). Joint pain and skeletal effects have been reported in persons exposed to high levels of aluminum, but these have generally been individuals with impaired kidney function who are unable to efficiently excrete aluminum in urine. Elevated brain concentrations of aluminum are also associated with Alzheimer's disease, although it is unclear whether elevated brain aluminum is a cause or symptom of the disease. In experimental animals, studies have also linked aluminum exposure to toxic effects in the central nervous system. Exposure of pregnant laboratory animals to aluminum has led to developmental problems in some studies and no problems in others. Developmental problems in humans have only been observed in babies with impaired renal function, in which brain and skeletal damage were noted. This group therefore represents a small but significant sensitive subpopulation at elevated risk from aluminum exposure.

Non-Cancer Health Risks: NCEA has established a provisional oral RfD of 1E+0 mg/kg/day, for aluminum. This is based on a LOAEL of 100 mg/kg/day, with a critical effect of minimal neurotoxicity in the offspring of mice. The co-critical studies used in establishing this LOAEL are the papers by Donald et al (1989), and Golub et al (1995), who dosed mice with dietary aluminum lactate (insoluble aluminum) during gestation and lactation. The neurotoxicity associated with
this LOAEL is consistent with LOAELs from other developmental and subchronic neurobehavioral studies in mice and rats which used higher dietary dosages of aluminum lactate or aluminum chloride. The LOAEL is considered minimal because the results of the post-weaning neurobehavioral test battery indicate that performance deficits may be marginal. NCEA has applied an uncertainty factor of 100 to this suggested RfD (3 for the use of a minimal LOAEL, 10 for interspecies extrapolation, and 3 for interhuman variability). Confidence in the co-critical studies is low.

EPA IRIS has thus far not established an oral RfD for aluminum due to the lack of clear animal or human data on aluminum toxicity. An RfD does exist for aluminum phosphide (a fumigant) but the toxicity addressed by the RfD stems from the phosphine gas liberated from this compound rather than from the aluminum. Similarly, the ATSDR declined to establish a minimum risk level (MRL) for aluminum due to the lack of evidence of adverse effects in humans and the overlap of NOAEL and LOAEL levels for neurological effects in animal studies. ATSDR noted that, using a LOAEL value with appropriate uncertainty factors, a MRL would be determined that is 10 times lower than the typical human dietary intake.

Carcinogenesis: The US EPA has not classified aluminum as to carcinogenicity (IRIS, 2000). Increased cancer incidence has been noted in workers in the aluminum industry, but this is believed to be due to exposure to other chemicals (e.g., PAHs) and not to aluminum. There do not appear to have been any adequate studies of the carcinogenic potential of aluminum in experimental animals.

NCEA suggests that aluminum be given a qualitative weight-of evidence as Group D (not classifiable as to human carcinogenicity), in accordance with the agency's proposed guidelines for carcinogenic risk assessment.

References

1. ATSDR (Agency for Toxic Substances and Disease Registry). 1997. Toxicological Profile for Aluminum (Update).
2. IRIS 2000. Integrated Risk Information System (On- line database)

Antimony: CASRN 7440-36-0

Antimony belongs chemically to the same periodic group as arsenic, and like arsenic, may be either trivalent or pentavalent. Antimony is a metal with numerous industrial uses, most of which are the result of antimony being mixed with various other metals to form alloys, or with oxygen to form antimony oxide. It is used in lead storage batteries, bearing metals, castings, pewter, sheet and pipe metal, and solder. The oxide is used in textiles and plastics to prevent them from catching fire. Historically, antimony was used medicinally as an anti-parasite agent, in treating leishmaniasis and schistosomiasis.

Like other metals, antimony occurs naturally in the environment. The ATSDR indicates that the normal background level of antimony in soil is less than 1 ppm, with high background being about 9 ppm. At hazardous waste sites and industrial sites where antimony wastes are processed, soil levels as high as 2550 ppm have been found. Exposure of the general population is largely from food, ATSDR indicates that the average daily intake of antimony via the human diet is about 5 micrograms per day.

The metabolism,–and in the very general sense, the toxicity-of antimony is somewhat similar to that of arsenic. It is absorbed slowly from the gut, and many antimony compounds are gastrointestinal irritants. Workers in antimony smelting and ore processing have noted various symptoms. Acute inhalation exposures result in irritation to the nose, pharynx and trachea, and can culminate in more serious respiratory problems leading to obstructive lung disease, pneumoconiosis and emphysema. Antimony-containing compounds can also affect the heart; this is evidenced from fatalities in certain patients who died from cardiotoxicity following treatment with antimony-based drugs. Workers with sufficient chronic exposure and/or sensitivity to antimony can also suffer transient skin eruptions, known as “antimony spots”.

IRIS lists an oral RfD of 4E-4 mg/kg/day, for antimony. This is based on a 1970 chronic dosing study of rats given potassium antimony tartrate in water. LOAEL from this study was 0.35 mg/kg/day. No NOAEL was derived from this study. Critical toxicologic endpoints were

longevity, and changes in blood glucose and cholesterol levels. Uncertainty factor is 1000, and confidence in the RfD is low.

At this time, EPA has not evaluated antimony in terms of carcinogenic potential.

Arsenic: CASRN 7440-38-2

This overview of the potential for human exposure to arsenic is provided from the current Agency for Toxic Substances and Disease Registry (ATSDR) publication in addition to other citations. Specific discussion about toxicity values used to characterize health risks potentially associated with exposure to inorganic arsenic is based on information provided in the U.S. Environmental Protection Agency (USEPA) Integrated Risk Information System (IRIS). Additional discussions of the current basis (i.e. skin cancer) for characterizing cancer risks were drawn from the reports prepared by the National Research Council and recent USEPA analyses of human epidemiological data.

Exposures to Arsenic: Arsenic is a common minor element in the earth's crust and is the 20th most abundant. Arsenic-bearing minerals are particularly concentrated in rock associated with metallic ore deposits, especially hydrothermally formed ore. In the Pacific Northwest, there are many reports of waterborne arsenic found in connection with historical mining of ore deposits, geothermal hot springs or areas where arsenic-rich igneous and sedimentary rocks have come in contact with ground water or surface water. While arsenic is released to the environment from natural sources such as these, releases resulting from man-made activities also exist. Examples of such man-made activities include mining, smelting, pesticide application, coal combustion, wood combustion, waste incineration and emissions resulting from refinement or combustion of crude oil or hydrocarbon fuels.

Low levels of arsenic are present in all environmental media and all living organisms. Arsenic exists in many chemical forms (chemical species), both organic and inorganic. These chemical species have varying toxicities ranging from practically non-toxic to very toxic. In humans, an ingested single dose of highly purified inorganic arsenic ranging from 50-100 milligrams or greater may result in acute poisoning which may be fatal. Environmental exposures are expected to be much lower. Concentrations in air in remote locations (away from human releases) range from 1 to 3 ng/m^3, while concentrations in urban areas may range from 20 to 100 ng/m^3. Concentrations in seawater are relatively homogeneous ranging between 1.5 to 5.0 ug/L with an

average of 1.7 ug/L. Concentrations in freshwater rivers and lakes vary widely and are dependent on the available minerals subject to transport. The average arsenic concentration in freshwater is approximately 1.7 ug/L with most waters ranging from 0.1 to 10 ug/L. Natural levels of arsenic in soil usually range from 1 to 40 ppm.

For most people, diet is the largest source of exposure. Arsenic is found in many foods at concentrations usually ranging from 20 to 140 ppb (total arsenic). However, total arsenic concentrations in rice, fish, shellfish and seaweeds many be ten times or more higher. The U.S. Food and Drug Administration which monitors the safety of the U.S. food supply states that the majority of dietary exposure to total arsenic is derived from seafood products. The identity of the chemical species of arsenic in seafoods is currently an area of active research and rapidly advancing knowledge. Certain lifestyle exposures may also be important sources of exposure such as the use of non-traditional medicinals, tobacco smoke, wine and hobby or artist's supplies. In regards to medicinals, for the last few centuries, inorganic arsenic has been used for a variety of health problems, particularly for asthma, rheumatic fever and skin conditions. Analyses of some present day herbal medicinals indicate concentrations of arsenic.

As mentioned above, the chemical species of arsenic have toxicities which range from very toxic to virtually non-toxic. Organic arsenic species (those with carbon molecules bonded to the arsenic) are less toxic and the inorganic arsenic species (those in which arsenic atom has a 3+ or 5+ charge and no carbon molecules; denoted as $As3^{+}$ or $As5^{+}$, respectively) are more toxic. Organic arsenic species such as arsenobetaine (AB), arsenocholine (AC), arsenosugars (AS), dimethyarsenic (DMA) and monomethylarsenic (MMA) predominate in foods. Because AB, AC and MMA are readily absorbed from the human digestive tract and excreted in urine rapidly and unchanged, these arsenic species are considered virtually non-toxic. In contrast, AS are apparently metabolized to DMA which is then excreted in urine. The USEPA has classified DMA as a category B2 carcinogen (probable human carcinogen based on sufficient animal, but insufficient human evidence) based on tumors in rodents.

In freshwater and marine water fish, shellfish and seaweeds, organic arsenic species may account for 90 to 100 percent of the total arsenic. Recognizing the significance of differentiating the inorganic versus organic content in seafoods, twenty years ago or more investigators in Europe, Australia, Asia and North America published analytical methods and their results. In recent years there has been concern about interconversion of the arsenic species throughout the analytical process, achieving reproducible and efficient recovery of all species, and loss of arsenic

concentrations during samples preparation. Recently published reports reaffirm previous findings of relatively low inorganic arsenic concentrations in finfish. In contrast, chemistry analytical methods are not adequate for determining accurate concentrations of AS and DMA in seafood.

Inorganic arsenic species taken up and retained by the body are initially distributed in greatest quantities to liver and kidney. Later on, as in chronic exposure, such inorganic arsenic tends to become biodistributed preferentially to highest concentrations in ectodermally-derived tissues such as hair, nails, and skin. Hair analysis is utilized by some clinicians as an rough indicator of overall inorganic arsenic body burden.

Toxicity of Inorganic Arsenic-Chronic Non-Cancer Health Effects: Effects in humans due to arsenic contaminated drinking water have been observed worldwide. Hence, toxicological information for development of the RfD is based on human exposures. The most distinguishing adverse effects associated with chronic ingestion of arsenic include skin changes and damage to the vascular system. Severe cases of chronic exposure result in a disorder known as "blackfoot disease", which is a progressive loss of circulation in the extremities ultimately leading to gangrene. The "blackfoot disease endemic area" in Taiwan had arsenic concentrations in well water ranging from 0.01 to 1.82 mg/L (Bates et al., 1992). The localized nature of blackfoot disease may be due to the presence of other substances consumed in drinking water (fluorescent substances) that are possible confounders or have caused synergistic effects (ATSDR, 1998; USEPA, 2000). While blackfoot disease has not been reported elsewhere in the world, other less severe signs of vascular injury (such Reynaud's disease) have been reported in other areas of the world). Hyperkeratosis, hyperpigmentation and skin cancer are also distinguishing adverse effects of arsenic exposure, and have been observed in populations in Taiwan, Mexico, India and Chile who consumed drinking water with high levels of arsenic (greater than 0.2 mg/L) . Hyperkeratosis and hyperpigmentation appear to be the earliest observable signs of chronic exposure.

Evidence of reproductive or developmental toxicity in humans is limited and inconclusive. The available studies in humans do not provide conclusive evidence that ingestion of arsenic, at the level usually encountered in drinking water, causes developmental toxicity. Studies in laboratory animals suggest that arsenic exhibits developmental toxicity (reduced birth weight, fetal malformations, and increased fetal mortality) at high levels of exposure (20 to 70 mg/kg-day, orally). The data suggest that inorganic arsenic does not pose a significant risk of developmental toxicity except at maternally toxic levels (ATSDR, 1998).

Genetic factors and age may distinguish human subpopulations that are sensitive to inorganic arsenic exposure, especially in their ability for metabolism. Metabolism involves processes associated with absorption into the body, distribution within the body, conversion of inorganic arsenic to another species of arsenic and elimination of arsenic from the body. Conversion of inorganic arsenic to an organic species enhances the water solubility of arsenic and facilitates urinary excretion. Theoretically, individuals with impaired capacity to produce water-soluble methylated arsenic metabolites may be at greater risk of adverse effects from arsenic exposure. Therefore, individuals with dietary deficiencies, impaired liver or kidney function may be more sensitive to adverse effects from arsenic exposure (ATSDR, 2000). Recently, it has been discovered that some methylated arsenic metabolites produced in the human body are more toxic then the initially ingested arsenic (Gregus et al, 2000; Aposhian et al 2000). One study in Finland suggests that children have lower arsenic-methylating ability than adults (Concha et al 1998). Hence, the overall significance of methylation of arsenic by the human body is still being worked out.

Development of the Non-cancer Oral RfD for inorganic arsenic: IRIS lists an oral RfD of 3E-4 mg/kg/day, for arsenic. Uncertainty factor is 3, and confidence in the RfD is medium. The Oral Reference Dose (RfD) is based on the occurrence of hyperpigmentation and hyperkeratosis, and vascular complications observed in the Taiwanese population ingesting elevated levels of arsenic in drinking water. The NOAEL was calculated to be 0.0008 mg/kg per day. An uncertainty factor of 3 is applied to account for both the lack of data to preclude reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals. The oral RfD for arsenic is 0.0003 mg/kg per day. According to USEPA, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.0001 to 0.0008 mg/kg per day. The RfD value used in this assessment was 0.0003 mg/kg per day.

Review of Cancer Health Effects: In terms of carcinogenicity, IRIS lists arsenic as Group A (known human) carcinogen. The oral carcinogenic slope factor for arsenic is 1.5E+0 mg/kg/day. The oral cancer slope factor for estimating excess the incidence of lifetime cancer risks due to inorganic arsenic is based on skin cancer observed in Taiwanese populations ingesting elevated levels of inorganic arsenic in drinking water. Doses were converted to equivalent doses for U.S. males and females based on differences in body weights and differences in water consumption. It was assumed that skin cancer risk in the U.S. population would be similar to the Taiwanese

population. It should be noted that USEPA's assessment is based on prevalence of skin cancer rather than mortality. The oral cancer slope factor is 1.5 (mg/kg-day) -1 .

Human exposures to inorganic arsenic in drinking water are also associated with cancers of the internal organs (lung, bladder, prostate, liver, kidney). The USEPA has not yet revised the oral cancer slope factor to account for the occurrence of internal cancers. However prior to the publishing the June 2000 proposal to lower the arsenic drinking water standard, the USEPA recently evaluated human epidemiological data for the incidence of bladder and lung cancer (65 FR 38888 and 65 FR 63027). The evaluations found the incidence of these cancers to be in the same range as the incidence for skin cancer (within a factor of 2 to 4).

As noted above in the overview, the extrapolation model assumes that the cancer response which occurs at higher exposures is the same at lower exposures. For inorganic arsenic, some scientific evidence suggests that this may be a faulty assumption and at low exposures the human body does not have an adverse cancer-producing response (USEPA 1997). However, no data exist to identify this theoretical exposure level.

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Barium: CASRN 7440-39-3

Barium is a metal which occurs naturally in the earth's crust. It is used industrially in the preparation of rubber, glass, tile, bricks, paints, etc. Barium is also used by the oil and gas industry to make drilling muds. With respect to barium toxicity, solubility is everything. In clinical settings barium sulfate, which is not soluble in the body, is sometimes injected into the bloodstream prior to X-Ray diagnosis, to enhance the visual depth of the images seen. But should soluble barium salts like barium chloride be used in this manner, death from heart failure can be instantaneous.

Barium is found at low levels in most soils and most food substances. It can be accumulated by aquatic organisms. Excess exposures to barium are usually workplace-related, or from the ingestion of contaminated water. Environmental levels also increase via the mining, refining and production of barium compounds, and from burning fossil fuels.

The oral RfD for barium is 7E-2 mg/kg/day. Previous investigations in research animals–both acute and chronic–have demonstrated the potential for hypertension to develop after high barium exposures. Based on these reports, lower dose human studies were undertaken to examine potential effects of barium exposure on blood pressure, EKG, and serum and urinary markers of toxicity. Although these studies unearthed no evidence of barium-induced human toxicity, an "adjusted NOAEL" of 0.21 mg/kg/day was developed. This dose, along with the findings of kidney effects seen from subchronic and chronic rat studies by the National Toxicology Program (NTP), serves as the basis for deriving the RfD, and is consistent with EPA's RfD methodology. An uncertainty factor of 3 is used to develop the RfD, to account for the lack of adequate developmental toxicity studies, and for the lack of data exploring potential differences between adults and children. Confidence in the RfD is medium.

In terms the of likelihood of barium being a carcinogen, adequate chronic oral exposure studies in mice and rats have not shown carcinogenic effects. EPA has thus classified barium in Group D (not classifiable as to human carcinogenicity.) However the lack of adequate inhalation exposure studies precludes the assessment of the carcinogenic potential of inhaled barium at this time.

Beryllium: CASRN 7440-41-7

Beryllium is one of the lightest metals known, and is found naturally in the mineral rock bertrandite, and also in beryl (the source of emerald and aquamarine). Although it occurs naturally in the earth's crust, its major emission source into the environment is via burning fossil fuels, especially coal, which releases beryllium containing particles into the air. It has important uses in the electronic and defense industries, especially in situations which require lightweight metals resistant to corrosion and fatigue. Beryllium oxide is also utilized in various high-technology materials which require resistance to heat.

Exposure to beryllium produces a wide range of health effects including lesions and sensitization. ATSDR indicates that a small percentage of the population is hypersensitive to beryllium. Although information about the oral toxicity of beryllium in humans is lacking in the literature, inhaled beryllium is extremely toxic to the lung. Chronic beryllium disease (beryllosis) in exposed workers is well documented, involving a progressive pulmonary granulomatosis. Beryllosis has a long latency period, and ATSDR indicates that even low and seemingly trivial inhalation exposures to beryllium may be important in causing it. Documented cases in the literature even point out occasional examples of beryllosis resulting from secondary contamination (e.g., a family member's exposure to beryllium from a worker's clothing).

The oral RfD for beryllium is 2E-3 mg/kg/day, based on a 1976 chronic dietary study in dogs, with the critical toxicological endpoint being the development of gastrointestinal lesions. Because a LOAEL and /or NOAEL were not clearly identifiable from the design and course of this study, dose-response modeling of the data was undertaken to derive a benchmark dose (BMD) for beryllium. A BMD10 (the lower 95% confidence limit on the dose from the maximum likelihood estimate (MLE) of a 10% relative change) of 0.46 mg/kg/day (MLE = 1.4. mg/kg/day) was derived for this lesion and used for further quantitation in this assessment. The uncertainty factor for the RfD is 300, and reflects a tenfold factor for interspecies differences, another tenfold factor for intraspecies variation, and a factor of 3 for deficiencies in the database. Confidence in the RfD, and in the supporting database, is low to medium.

In terms of carcinogenicity, EPA has classified beryllium in Group B1 (Probable Human Carcinogen), by inhalation. Studies regarding the potential carcinogenicity of ingested beryllium to humans were not available. ***For purposes of this report, beryllium will not be considered to be a potential carcinogen via the oral route of exposure.***

Cadmium: CASRN 7440-43-9

Cadmium is a metallic element that is naturally present at low levels in rocks and soils. Cadmium is introduced into the environment by both natural processes or industrial activities such as combustion of fossil fuels or metal mining and refining (ATSDR, 1997). Cadmium is found in a variety of products including nickel-cadmium batteries, pigments in paints, plastics and ceramics, polyvinyl chloride (PVC) products (as a stabilizer) and in various metal alloys (ATSDR, 1997). Foodstuffs typically contain small amounts of cadmium with the highest amounts in leafy vegetables and potatoes (ATSDR, 1997). The typical daily intake of cadmium from food is about 30 ug/day (ATSDR, 1997). Tobacco and cigarette smoke also contain significant amounts of cadmium and the daily intake of cadmium may be increased an additional 1 to 3 ug/day for each pack of cigarettes smoked (ATSDR, 1997). Cadmium does not appear to be an essential nutrient.

Unlike many other toxic metals, toxic effects from cadmium are more straightforward, since cadmium does not combine with organic ligands to form organometallic compounds. Exposure to cadmium may be evaluated by looking at cadmium levels in biological matrices such as blood, hair, nails and urine.

Studies in humans have indicated that the amount of cadmium absorbed into the body after oral exposure ranges from about 5 to 10 percent (ATSDR, 1997). Iron status affects cadmium absorption and persons with iron deficiency may absorb more cadmium. After absorption, cadmium is distributed throughout the body with the largest accumulation in the liver and kidney (ATSDR, 1997). Cadmium is excreted very slowly once it is deposited at these tissue sites, with elimination half-times on the order of years rather than days or weeks. Cadmium is a classic lifetime cumulative poison, accumulating in the kidney throughout life.

Accordingly, chronic exposure leads to renal accumulation and kidney degeneration (ATSDR, 1997). It also causes bones to become brittle and easily damaged. These effects have been reported in human populations with elevated levels of dietary cadmium due to high levels of cadmium in soils. Similar effects have been noted in experimental animals. Chronic cadmium exposure may also interfere with iron uptake and has lead to anemia in experimental animals. In animals, chronic exposure to cadmium has also lead to neurological impairments and a limited amount of evidence for such effects have also been observed in human populations (ATSDR, 1997). Exposure of pregnant laboratory animals to cadmium has resulted in some developmental problems, particularly CNS development.

Non-Cancer Health Risks: EPA has established two oral RfDs for cadmium: For cadmium in food, the RfD is 1E-3 mg/kg/day. For cadmium acquired from drinking water and potable water sources, the RfD is 5E-4 mg/kg/day, respectively. The two values are based on the different GI absorption of cadmium from food and water. ***For purposes of this report, which assesses risk from ingesting fish tissue, the RfD for cadmium will be assumed to be 1E-3.*** **mg/kg/day.**

Toxicological data for establishing the respective RfDs come from an EPA analysis of human data (US EPA, 1985) which found that a kidney concentration of 200 ug/gm was the highest renal level not associated with adverse effects (specifically proteinuria; as evidenced by elevated beta-2 microglobulin in urine, etc.) NOAEL (from water-derived exposure) was 0.005 mg/kg/day. NOAEL (from food-derived exposure) was set at 0.01 mg/kg/day. Using a toxicokinetic model, a safe intake level of 0.01 mg Cd/kg/day from food was then estimated. The estimated NOAEL was divided by an uncertainty factor of 10 to account for sensitive subgroups in the human population. Confidence in the RfD is high due to the large amount of human and animal toxicology data available for this compound.

Carcinogenesis: The EPA has determined that cadmium is a probable human carcinogen (Class B1; IRIS, 2000), by the inhalation route. This is largely based on inhalation studies in occupationally exposed populations and on inhalation and oral dose studies in experimental animals.

Although there are sufficient experimental and epidemiologic data to derive inhalation unit risk values for cadmium, there does not appear to be sufficient evidence to derive oral slope factors. As a consequence, the carcinogenicity of cadmium following oral exposure remains controversial.

Accordingly, no oral carcinogenicity slope factor has been calculated for cadmium. ***For purposes of this report, cadmium will not be considered to be carcinogenic by the oral route of exposure.***

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Chromium (+6): CASRN 18540-29-9

Chromium exists in two possible valence states (Chromium +3, and Chromium +6) Trivalent chromium (Cr+3) is regarded to be an essential nutrient, while Hexavalent Chromium (Cr+6) is a known human carcinogen, by inhalation.

For purposes of this report, all chromium reported in the various analyses as "total chromium" will be considered to be Cr+6. This is no doubt an overstatement of the actual risk, because it is unlikely that all of the chromium detected in the various fish samples would actually be the Cr+6 species.

Hexavalent Chromium (Cr +6) has an oral reference dose of 3E-3 mg/kg/day. This RfD is based on a one-year drinking water study in rats, from 1958. The NOAEL from this study was assumed to be 2.5 mg/kg/day, adjusted from a dose of 25 mg/l of chromium administered daily as potassium dichromate. Although the rats did abruptly accumulate significant amounts of excess chromium during the study, they did not exhibit noticeably significant adverse effects at the doses administered. From this it was assumed that apparently the rodent tissues can accumulate considerable quantities of chromium before pathological changes result. Accordingly, no LOAEL was developed for chromium on the basis of these data. Uncertainty factor is 300. This includes
two tenfold factors to account for both the expected interhuman and interspecies variability in the toxicity of the chemical in the absence of specific data, and an additional factor of 3 to compensate for the less-than-lifetime exposure duration of the principal study. An additional modifying factor of 3 is also used, to account for concerns raised by a more recent study of humans exposed to hexavalent chromium in China. This (1987) Chinese study suggests that humans may suffer gastrointestinal effects following exposure to levels of around 20 ppm hexavalent chromium in drinking water. Confidence in the RfD is low.

IRIS lists Cr+6 as a Group A (known human) carcinogen, by inhalation. Because of this, no oral carcinogenic slope factor has been calculated for Cr+6.

Cobalt: CASRN 7440-48-4

Cobalt is a relatively rare metal, whose principal source is as a by-product of other metals, chiefly copper. It is used in permanent magnets, and in high-temperature alloys. Cobalt salts are useful in paint dryers, as catalysts, and in the manufacture of various pigments.

Cobalt is a metal which has both beneficial and deleterious effects, depending on the exposure route, dose, and the type of biochemical /pharmacological pathway with which these doses and exposures are associated. For example, cobalt is essential as a component of vitamin B12, required for the production of red blood cells and prevention of pernicious anemia. Deficiency diseases of ruminant animals, caused by inadequate natural levels of cobalt in the diet, are characterized by anemia, weight loss, and retarded growth. Cobalt's ability to stimulate the production of red blood cells in humans has led to its frequent use as a treatment for anemia.

In terms of its toxic effects, probably the most well known and most serious effects of cobalt overdose have been evidenced in the late 1960's and early 1970's, when a high incidence of "beer-cobalt cardiomyopathy" was reported in certain groups of people who drank large quantities of beer containing cobalt chloride, which had been added as a stabilizer to control foaming. (Since then, the practice of adding cobalt to beer as a foam stabilizer has been abandoned). It should be noted, however, that the cardiomyopathy may have also been exacerbated by the fact that the beer-drinkers had protein poor diets and may have had prior cardiac and hepatic damage from alcohol abuse. In support of this possibility, peripheral studies of anemic patients treated with comparable-or even much higher-doses of cobalt did not results in cardiac effects. Cobalt has also been found to be a sensitizer in humans. Individuals can become sensitized following dermal or inhalation exposure, but it has also been shown that oral ingestion of cobalt can trigger flares of dermatitis in patients with pre-existing eczema. There is also an interrelationship between cobalt sensitization and nickel sensitization. Orally administered cobalt has also been found to cause
fetal effects in pregnant rodents, but these effects occurred at dose levels that were so high as to be maternally toxic. In addition, several studies have reported testicular degeneration and atrophy in rats exposed to 5.7 to 30.2 mg cobalt/kg/day for 2-3 months in the diet or in the drinking water. In summary, human data indicate that cobalt does not appear to manifest toxicological symptomology except in unusual circumstances of exposure (i.e excessive oral exposure via the contaminated beer episode, or through occupational sensitization)

Given the contradictory nature and complexity of the various data for cobalt and its biological endpoints–both harmful and beneficial–NCEA indicates that although the existing cobalt data do

not identify a single conclusive animal or human study from which one could properly derive an oral RfD, the most sensitive indicators of cobalt toxicity following oral exposure are (1) the increase in hemoglobin in both humans and animals, and (2) the elicitation of dermatitis in sensitized individuals. NCEA indicates that the upper range of average intake for children (0.06 mg/kg/day) is below the levels of cobalt needed to induce polycytemia in both renally compromised patients (0.18 mg/kg/day), and normal patients (0.96 mg/kg/day). Based on this, and given the ubiquitous nature and the relatively well characterized intake of cobalt in food, NCEA recommends that the intake levels described above be used as guidance for an oral exposure to cobalt. Accordingly NCEA has suggested a provisional oral RfD of 6E-2 mg/kg/day for cobalt.

At this time, EPA has not evaluated cobalt in terms of possible carcinogenicity.

Copper: CASRN 7440-50-8**.**

Copper is a metallic element and a natural component of the earth's crust. Copper can enter the environment either though natural process or human activity, such as copper smelting or ore processing (ATSDR, 1990). Copper is used extensively in industry in components such as wiring and water pipes. Copper is also used in alloys with other metals; for example bronze is an alloy of copper and tin while brass is an alloy of copper and zinc. Copper compounds may be used in to treat certain plant diseases or as a wood preservative. Copper is an essential dietary element for animals and humans and is present in many vitamin supplements. The recommended daily allowance (RDA) for copper, the amount that should be present in a healthy diet, is 1.5 to 3 mg/day (NRC, 1989). Food and drinking water normally contain very small amounts of copper that are sufficient to meet the body's need for this element. Exposure to copper may be assessed through urinary or blood measurements.

Copper is readily absorbed in the body across the GI tract, although the degree of absorption may depend on the material with which it was ingested. Normally, the body has several ways to prevent copper overload but in individuals with Wilson's disease, these mechanisms are not fully functional. Persons with Wilson's disease may therefore be particularly susceptible to copper toxicity.

While some amount of copper is required to maintain a healthy body, higher doses of copper may result in toxicity. The primary symptoms of exposure to high doses of copper are acute in nature;

centering on the GI tract, with vomiting, nausea, diarrhea and loss of appetite (ATSDR, 1990). Liver and kidney effects have also been reported in both and animals exposed to copper (ATSDR, 1990). These symptoms have been reported in humans across a wide range of doses, from 0.07 to 1,421 mg/kg/day (ATSDR, 1990). The form in which the copper was ingested (e.g., in food, drinking water, alcohol) may be in part responsible for this wide range in sensitivity.

Non-Cancer Health Risks: The oral RfD for copper in the IRIS risk database has been withdrawn, pending further evaluation. This value was based on a report of acute copper toxicity in humans that has been questioned on methodological grounds. However, HEAST lists a derived oral RfD of 3.7E-2 mg/kg/day, for this metal. This oral RfD value for copper was derived by the EPA Environmental Criteria and Assessment Office as part of the Drinking Water Criteria Document For Copper (1985). This is based on their calculations and underlying LOAEL assumptions used in deriving the Drinking Water 1-Day Health Advisory of 1.3 mg/l (which is also the recommended level for the Lifetime adjusted acceptable daily intake (AADI)). Copper is an essential element in the diet. There are no data indicating that human exposure to copper results in chronic toxic effects. The available human studies all suggest that the ingestion of between 5.3 and 32 mg copper/person, in a single acute dose, results in gastrointestinal disorders, vomiting, nausea and diarrhea. No lasting adverse effects were reported over this dose range. Moreover, both animal and human data support the concept that the effects of concern from exposure to copper appear to be acute, not chronic, and that the effects (which at the lowest effective doses in laboratory rodents are on the liver and kidney, rather than on the G-I tract) appear reversible as long as the daily dose is not a relatively massive one. In rats, for example, feeding
2000 mg/kg/day of copper sulfate results in periportal hypertrophy of the liver parenchymal cells after about 2 weeks of dosing, with symptoms most severe at week 6. Kidney histopathology was also noted. However, after 15 weeks of exposure at this dose, almost complete recovery was observed for both organs.

Therefore, in developing the drinking water criteria document for copper (1985), the EPA Environmental Criteria and Assessment Office has utilized the lowest single oral human dose given in the available literature--5.3 mg--as the LOAEL for human exposure. Dividing this by 2 liters intake per day, and using an uncertainty factor of 2, gives the recommended 1-Day Health Advisory, (and ADDI calculation) of 1.3 mg/l. Such a low uncertainty factor is applied because: (1) the key toxic symptom was local G-I irritation, and was not permanent, with no long term

effects reported, (2) 5.3 mg/day was the lowest value determined in the literature based on several studies. It was based on fasted subjects, and is thus very conservative, (3) copper is an essential element, and the use of a larger safety factor would bring the level below that considered necessary for human nutrition, and (4) copper absorption is controlled by a hemostatic mechanism, and–in normal individuals-does not accumulate in the body. Calculating back from the Health Advisory of 1.3 mg/l, for a 70 kg person drinking 2 liters of water per day, the "derived RfD" would thus be 0.037 mg/kg/day, or 3.7E-2 mg/kg/day. Critical human toxicologic endpoint for the RfD is G-I irritation.

Exposure of laboratory animals to high concentrations of copper (greater than 100 times the RDA) has produced some birth defects. These effects have not been observed in exposed human populations.

Carcinogenesis: The USEPA has determined that there is insufficient evidence to classify copper as to carcinogenicity (IRIS, 2000). Several animal studies have yielded conflicting results and are of insufficient strength to make a clear determination of carcinogenicity.

Lead: CASRN 7439-92-1

A great deal of human and animal data are available regarding the toxicity of lead. Lead ions are very similar to calcium ions, in terms of size and shape. It follows that metabolically, throughout one's lifetime, about 95 per cent of lead which remains in the body eventually becomes deposited in compact bone. However, because of the way lead is taken up and distributed within the various hard and soft body tissues, risk and toxicity to humans from lead is measured as a function of blood lead level(s). At this time, no oral RfD for lead, has been established by IRIS This section summarizes lead health studies which relate adverse health effects to blood lead concentrations.

For children, 10 micrograms per deciliter (µg/dl) is the blood lead concentration of concern. A blood lead concentration of below 10 µg/dl is an acceptable level of exposure (U.S. Environmental Protection Agency, 1994; U.S. Environmental Protection Agency, 1998). The level of 10 µg/dl is based on children's IQ scores and other functional deficits associated with elevated blood lead levels. Lead health studies have been summarized in several comprehensive reviews prepared by: (Centers for Disease Control and Prevention, 1991) (National Research

Council Committee on Measuring Lead in Critical Populations, 1993); (U.S. Department of Health and Human Services, 1999). A threshold below which lead does not affect IQ in children has not been established and a Reference Dose (RfD) is not appropriate for lead.

Sensitive People: Sensitive groups include developing embryos/fetuses/neonates, young children, women, and individuals with chronic neurological dysfunction or kidney disease. Older adults are at risk of hypertension aggravated by lead (National Research Council Committee on Measuring Lead in Critical Populations, 1993). From gestation through the first three years of life, children have an incompletely developed blood-brain barrier and their rapidly developing nervous system is very sensitive to the effects of lead (Rodier, 1995). Lead can increase the permeability of the blood-brain barrier to further increase exposure at the target tissues. The transfer of maternal lead during pregnancy and lactation and normal oral exploratory behaviors increase exposures lead in soil and house dust during this vulnerable period (Goldstein, 1990); (Mushak, 1998). Young children are at risk because compared to adults they absorb more lead from the gastrointestinal tract; retain more absorbed lead; have a greater prevalence of nutritional deficiencies (e.g., calcium, iron, and zinc), which increase both the absorption and the toxic effects of lead. Women who are pregnant, are lactating, or have osteoporosis may be themselves at greater risk due to lead because each of these conditions may intensify the mobilization of lead from bone.

Neurological Effects: Death from encephalopathy has been reported in children and adults with blood lead concentrations as low as 80 and 100 μg/dl, respectively (National Research Council Committee on Measuring Lead in Critical Populations, 1993). IQ decrements, altered behavior, peripheral neuropathy, hearing impairment, reduced motor nerve conduction, and fine-motor dysfunction have been observed in children (Ibid.). Lead causes similar dose-dependent neuro-toxic symptoms in adults from encephalopathy, to less severe cognitive impairments, and peripheral neuropathy (Ibid.).

Hematological Effects: Lead interferes with heme synthesis. Reduction of the heme body pool can lead to adverse effects in several physiological systems. Anemia can result from decreased hemoglobin production and increased red blood cell destruction. Lead-induced inhibition of heme synthesis can interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. There is no apparent threshold for indicators of decreased heme synthesis (U.S. Department of Health and Human Services, 1999).

Developmental and Fetal Effects: Lead in maternal blood is shared with the fetus and breast milk can be a significant source of lead for infants (Mushak, 1998). Women with occupational exposures to lead during pregnancy have an increased rate of miscarriages and stillbirths. (Bornschein, Grote, Mitchell, Succop *et al*., 1989) have identified lead-induced reductions in birth weight, gestational age, and stature in children.

Male Reproductive Effects: In men with occupational lead exposures, decreased sperm count, abnormal sperm morphology, decreased sperm mobility, and hormonal changes have been observed (Alexander, Checkoway, van Netten, Muller *et al*., 1996).

Acute Effects: In addition to encephalopathy, acute (reversible) nephropathy can occur during the early stages of high exposure to lead. Chronic (irreversible) nephropathy can also occur. Acute exposures to high levels of lead can produce cardiac lesions, electro-cardiographic abnormalities, and hemolytic anemia in children and adults (National Research Council Committee on
Measuring Lead in Critical Populations, 1993). Colic is a symptom of severe or clinical lead poisoning. Analysis of U.S. National Health and Nutrition Examination Survey II (NHANES) epidemiological data shows hypertensive effects in the form of elevated systolic and diastolic blood pressure in older adults at blood lead levels below 25 µg/dl (Ibid.).

Carcinogenesis: The oral carcinogenic slope factor for lead is currently under review by EPA.

EPA has classified lead in Group B2 (Possible Human Carcinogen). However, at this time, no carcinogenic slope factor has been developed for lead.

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Manganese: CASRN 7439-96-5.

Manganese is a metallic element that is naturally present at low levels in the earth's crust. Manganese can enter the environment either though natural processes or industrial sources such as coal burning power plants or steel foundries (ATSDR, 1996). Manganese and manganese compounds are used in the production of steel, batteries, dietary supplements, ceramics, pesticides and fertilizers (ATSDR, 1997). Food and drinking water normally contain low amounts of manganese. Trace levels of manganese are needed in the normal diet because manganese is a component of several important enzymes. The estimated safe dietary intake for manganese ranges from 0.3 to 5 mg/day, depending on age (NRC, 1989). Exposure to manganese may be assessed measurement of several biological matrices, including blood and urine.

Manganese appears to be only incompletely absorbed in the GI tract after ingestion. Studies in animals and humans have suggest that up to 5% of the manganese dose is absorbed (ATSDR, 1997). Manganese is eliminated from the body, primarily in the feces, with half-times reported to range from 13 to 37 days (ATSDR, 1997).

While small amounts of manganese are necessary for good health, higher doses may lead to toxicity. Workers who have been exposed to high levels of manganese through inhalation have developed emotional or mental disturbances and problems with body movements in a syndrome known as manganism. Impotence has also been reported in men occupationally exposed to high levels of manganese by inhalation. Evidence that these effects also occur in humans from oral exposure to manganese is much weaker, but studies in animals have shown that very high levels of manganese in the diet can cause brain disturbances or testicular damage. These effects in animals occurred at doses 100 to 1000 times higher than the typical daily intake for humans. There is inadequate information to determine whether manganese exposure causes toxicity in developing animals when exposed *in utero.*

Non-Cancer Health Risks: The oral RfD for manganese is 1.4E-1 mg/kg/day. The RfD is based on estimates of dietary intakes in various human populations. Although the critical toxicologic endpoint in deriving this RfD was centered upon epidemiologic evaluation of evidence for effects on the central nervous system ("mangenism"), the populations studied did not appear to exhibit adverse effects of manganese exposure (IRIS, 2000) at the doses levels under consideration. From these studies, EPA determined that 10 mg/kg/day represents an upper bound on the normal dietary intake for manganese. This is equivalent to 0.14 mg/kg/day for a 70 kg individual. Because the data are derived from human populations, no modifying or uncertainty factors are used.
Confidence in the RfD is medium, based upon the many human epidemiologic studies used in derivation. Uncertainty factor is 1. However, some concerns remain about potential sensitivity in specialized populations.

Carcinogenesis: The USEPA has determined that there is insufficient evidence to classify manganese as to carcinogenicity (IRIS, 2000). Several studies have suggested an increase in tumors after exposure to manganese compounds but the data has been characterized as "equivocal", typically due to a weak dose-response relationship (ATSDR, 1997).

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Methylmercury: CASRN 22967-92-6

Inorganic mercury compounds include elemental mercury metal (Hg0), and its various

divalent/trivalent mercury salts. Mercury compounds undergo global biogeochemical cycling in the environment, especially in freshwater aquatic ecosystems, in which inorganic mercury is methylated by microorganisms to form the much more toxic organic form, methyl mercury (MeHg). In the pregnant female, methyl mercury can impact the developing fetus by crossing the placenta and the blood-brain barrier, where it can cause serious neurological and other consequences by interfering with cell division in the developing brain, and by affecting the development of the embryonic neural crest.

Methyl mercury undergoes significant bioaccumulation in all aquatic food webs. It has also entered the environment historically as a by-product of the plastic industry, and (along with ethyl mercury) as a fungicidal dressing for seed grains. Approximately 90 percent of the mercury in biological organisms is considered to be sequestered in the form of methyl mercury, and the main dietary source of methyl mercury in the environment is believed to come almost exclusively from fish. Thus, organic mercury (rather than metallic mercury per se) is considered more relevant to fish contamination and is subsequently used for toxicity analysis in most environmental risk assessments.

Short chain alkyl mercurials like MeHg have a half-life in man of approximately 65 days. In the body, these short chain alkyl mercury compounds tend to be found in at higher levels in ectodermally-derived tissues like skin, and especially hair. In recent years, hair has become a fairly reliable dosimeter among many toxicologists for estimating body burden of organic mercury. The mean hair level (as total mercury) for the normal US population is estimated to be about one part per million (ppm). The World Health Organization "Safe Limit" for hair is about 5 ppm. Extreme fish eaters have shown hair mercury levels as high as 170 ppm.

The current oral RfD for methyl mercury is 1 x E-4 mg/kg/day (0.1 ug/kg/day). It is based on a study of widespread human exposure to this compound during 1971-72 in Iraq, in which methylmercury treated seed grain was mistakenly used in home-baked bread. The critical toxicologic endpoints in this assessment were developmental and neurological abnormalities in human infants. A benchmark dose was used rather than a NOAEL/LOAEL approach to analyze the neurological effects in infants as the response variable. Uncertainty factor is 10, and confidence in the RfD–and its supporting database--is medium.

At the request of Congress, In July 2000, EPA's RfD for methyl mercury was thoroughly reviewed by the National Academy of Science (NAS). This included an extensive review of new

research findings which have emerged since EPA's current RfD was developed in 1995. The NAS analyzed more recent and comprehensive studies of fish-eating populations in the Faroe Islands, Seychelle Islands, and New Zealand. NAS concurred with EPA's RfD of 0.1 ug/kg/day, but also concluded that the Faroe Islands analysis should now be used as the critical study for deriving this reference dose.

The potential for carcinogenicity of mercury and mercury compounds is currently under review by EPA.

Nickel: CASRN 7440-02-0

Nickel is a metal which is quite abundant in the earth's crust. Nutritionally, it is believed to be an essential trace metal required to maintain health in animals. Casarret and Doull indicate that over the past few years, evidence is mounting that nickel may be a nutritionally essential trace metal in the diet of humans as well. In the environment, nickel is predominantly found in soil and sediment, usually in association with iron or manganese. In general, nickel does not appear to significantly bioaccumulate in fish, plants, or animals used for food. Metallic nickel combines with other substances to form various nickel sulfides, nickel carbonyl, and other nickel compounds, some of which are of considerable toxicological importance in the occupational or industrial setting. Nickel carbonyl--Ni(CO)4–is the most toxic form, with many reports of serious and potentially fatal gastrointestinal and respiratory consequences following acute workplace exposures. Another nickel compound, nickel subsulfide –Ni3S2– is a carcinogen in humans via inhalation.

IRIS does not list a specific RfD for metallic nickel, per se. Rather, the oral RfD is derived for "nickel soluble salts". This oral RfD for nickel soluble salts, is 2E-2 mg/kg/day. It is based primarily on a two-year feeding study in rats, (presumably) dosed with dietary nickel as the chloride salt, in which body and organ weights of both sexes were significantly decreased at the high dose levels. LOAEL from this study was 50 mg/kg/day (100 ppm in the diet). NOAEL was 5 mg/kg/day (10 ppm in the diet). Similar dietary exposure studies in dogs resulted in depressed body weight gain at about 63 mg/kg/day (2500 ppm nickel in the diet), but no effects were noted

at lower doses. It is thus likely that the rat is the more sensitive of the two species. Uncertainty factor is 300. Confidence in the data is medium.

In addition to the effects on organ weights described in the critical study, two other sensitive toxicological endpoints exist for nickel. These are neonatal mortality, and dermatotoxicity. While no reproductive effects have been associated with nickel exposure to humans, several studies in laboratory animals have demonstrated fetotoxicity. Nickel is also a well-known contact irritant to skin (e.g., from jewelry). In addition, many studies have also demonstrated dermal effects in sensitive humans resulting from ingested nickel. For such hypersensitivity reactions, it is accordingly difficult to establish a dose-response relationships.

Soluble salts of nickel have not been evaluated by the EPA in terms of potential carcinogenicity. However, nickel refinery dust and specific nickel compounds–nickel carbonyl and nickel subsulfide–have been evaluated. Some of these compounds–which are found in certain occupational exposures in industrial situations-are classified as possible probable human carcinogens by inhalation. Summaries of these evaluations are on IRIS.

For purposes of this assessment, nickel acquired dietarily from fish tissue is not considered to be a carcinogen, and no data exist to indicate otherwise.

Selenium: CASRN 7782-49-2

Selenium is a metallic element and a natural component of the earth's crust. Selenium can enter the environment either though natural process or human activity, chiefly the burning of coal or oil (ATSDR, 1996). Selenium is present in small amounts in plastics, paints, fungicides, certain types of glass, anti-dandruff shampoos, and photographic supplies (ATSDR, 1996). Selenium is also an essential dietary element for animals and humans and is present in many vitamin supplements. The recommended daily allowance (RDA) for selenium, the amount that should be present in a healthy diet, is 0.055 mg/day for women and 0.070 mg/day for men. While small amounts of selenium are required to maintain a healthy body, higher amounts of selenium may cause toxicity. Toxic effects of selenium have been reported at levels only 5 to 10 times the RDA (ATSDR, 1996).

Although elemental selenium and its selenate (Se4+) salts are insoluble, selenates (Se+6)–much in the manner of sulfates-, and are readily taken up by biological systems. After initial exposure,

highest accumulation is initially in the liver and kidneys. Long term exposure to selenium may result in selenosis, resulting in brittle hair and fingernail deformities, and at more serious levels, loss of sensation in the arms and legs. Exposure to selenium in humans may be assessed through urinary or blood selenium measurements. Exposure of laboratory animals to very high concentrations of selenium (hundreds of times the RDA) has also resulted in birth defects. These effects have not been observed in exposed human populations.

Non-Cancer Health Risks: The oral RfD for selenium is 5E-3 mg/kg/day, or approximately 5 times the RDA. This value was established based on the study of Yang et al. (1989) which documented selenosis in a human population with long term exposure to selenium. This study was conducted in a region of China with unusually high levels of naturally occurring selenium in groundwater and soil. Critical effects noted included: liver dysfunction and clinical signs of selenosis (such as hair or nail loss, morphological changes of the nails, etc. Chronic toxic effects include lowered hemoglobin levels, mottled teeth, skin lesions and CNS abnormalities. In this study, no effects were observed at an estimated intake of 0.015 mg/kg/day (NOAEL), though effects were observed at a level of 0.023 mg/kg/day (LOAEL), highlighting the limited range over which toxicity may ensue. An uncertainty factor of 3 is used to account for sensitive individuals. Confidence in the RfD is high, based upon the many animal studies and epidemiologic studies supporting the principal study.

Carcinogenesis: Most selenium compounds are not believed to cause cancer (IARC, 1987) although there is a lack of human data and the results of several simple screening tests are contradictory (IRIS, 2000). Some studies also indicate that animals treated with low levels of selenium had a reduced risk of cancer relative to animals that received no selenium, further complicating interpretation of the study results. The existing cancer data for selenium are thus conflicting and equivocal. For this reason, IRIS lists selenium in group D (not classifiable as to carcinogenicity).At this time there is thus no credible evidence for considering selenium to be a carcinogen.

Selenium Sulfide: CASRN 7446-34-6

At this time, no oral RfD has been developed for selenium sulfide. However, it is reasonable to assume that the sulfide form of selenium would exert its various higher-dose non-carcinogenic toxicologic effects in a mechanism similar to that outlined above for other selenium compounds.

In contrast to other selenium compounds, however, selenium sulfide, has been classified by EPA as a probable human carcinogen (Class B2). Human evidence is inadequate/lacking. The classification is based on long term exposure studies using laboratory mice, in which liver and lung tumors were noted. It is important to note that animals in these studies were given selenium sulfide at concentrations over 100 times the RDA for selenium and therefore well above likely human exposures. In addition, selenium sulfide compounds are generally water insoluble and would pose limited risk of exposure via drinking water or other water mediated pathways (i.e., fish contamination).

Despite the B2 classification as to likelihood of carcinogenicity for this compound, no oral carcinogenic slope factor has been developed for selenium sulfide at this time.

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Silver: CASRN 7440-22-4

Silver is not considered to be significantly toxic at normal levels of environmental exposure, nor does it normally occur at significant levels in human or animal tissues. Silver is also used medicinally; e.g., the historic and widespread use of silver nitrate as a prophylactic treatment for eye infections in the newborn. Other medicinal uses of silver salts include various preparations utilized as germicides, antiseptics, astringents, and caustics.

Large oral doses of silver nitrate cause severe gastrointestinal irritation, due to its caustic action. The critical toxicologic effect in humans ingesting sufficiently high doses of silver is argyria, a medically benign, but permanent bluish-gray discoloration of the skin. Argyria results from the deposition of silver in the dermis, and also from silver-induced production of melanin.

The oral RfD for silver (as silver nitrate) is 5E-3 mg/kg/day, with the critical toxicologic endpoint of argyria, as evidenced in a 1935 study of intravenously-dosed humans. No NOAEL was established for this endpoint. However, IRIS cites a derived a LOAEL of 0.014 mg/kg/day. This was based on a 1 gram total dose (administered as 4 grams silver arsphenamine), and based on conversion from the total i.v. dose to a total oral dose of 25 grams (see IRIS for specifics) and dividing by 70 kg (adult body wt.), and 25,500 days (a lifetime, or 70 years) of exposure. The RfD has an uncertainty factor of 3. Despite this, confidence in the RfD is low, because all but one of the individuals in the human study did not develop argyria until a fivefold greater LOAEL dose level had been administered.

Silver is not considered to be a carcinogen. EPA has classified silver in Group D (not classifiable as to human carcinogenicity).

Thallium: CASRN 7440-28-0

Thallium is a metallic element and a natural component of the earth's crust. Thallium can enter the environment either though natural process or human activity; low levels of thallium are produced during the burning or coal, the production of cement and the smelting of certain metals (ATSDR, 1992). Thallium may be used in electronic components, certain types of glass and specialized medical procedures to investigate heart disease (ASTDR, 1992). Thallium has also been used historically as a potent rodenticide.

Thallium is not believed to be an essential nutrient, and is not a normal constituent of animal tissues. In the body, thallium distributes much in the same fashion as potassium, which probably accounts for its propensity toward neurological effects as sufficiently high doses are reached. Thallium is one of the more toxic metals, and can cause injury to the nervous system, liver, and kidney. There is limited knowledge about the low-dose toxicity of thallium to humans and only a few studies in laboratory animals. Studies in both humans and animals suggest that thallium is well absorbed across the GI tract. Thallium is eliminated from the body fairly slowly in humans, with the reported half-life from one study reported as 22 days (ATSDR, 1992). Thallium is distributed–much like potassium-throughout the body, with the liver, kidney, heart and skin being the primary targets for this chemical. Highest concentrations after acute doses are in urine and kidney. Exposure to thallium may be assessed through evaluation of hair or urine. At levels of exposure above 1 mg/kg/day in laboratory animals, thallium is known to damage the nervous system and cause loss of hair (alopecia). Thallium has not been shown to be a specific

developmental toxicant, that is, one that is capable of causing birth defects in the unborn child at levels that do not harm the mother. Low levels of thallium exposure in rats have resulted in altered sperm and testicular function. These results have not been observed in humans.

Non-Cancer Health Risks: USEPA has developed reference doses (RfDs) for specific thallium compounds. The available RfDs are:

Thallium acetate	9E-5 mg/kg/day
Thallium carbonate	8E-5 mg/kg/day
Thallium chloride	8E-5 mg/kg/day
Thallium nitrate	9E-5 mg/kg/day
Thallium sulfate	8E-5 mg/kg/day

RfDs are not available--or have been withdrawn--for thallium oxide and thallium selenite. ***For purposes of this report, the RfD for thallium will be assumed to be 9E-5 mg/kg/day, using the supporting toxicological data for thallium nitrate, as evidenced in a 1986 oral subchronic study in rats.***

Although compound-specific, the RfDs are all based the results of a study involving thallium sulfate with appropriate adjustment for differing molecular weights between different thallium compounds. The thallium sulfate study (EPA, 1986) involved administration of the compound to rats for 90 days. Limited loss of hair and changes in some blood chemistry parameters were observed, but these were not determined to be serious adverse effects. Critical toxicologic endpoints were elevated levels of critical enzymes (SGOT and LDH) associated with liver function changes. The NOAEL of 0.25 mg/kg/day (the maximum study dose) was divided by an uncertainty factor of 3000 to arrive at the RfD. Another study (Formigli et al., 1986) observed testicular degeneration at a thallium sulfate dose of 0.7 mg/kg/day (30 to 60 day treatment) suggesting that the threshold for that particular toxic endpoint is also fairly close to the NOAEL. Confidence in the RfD is considered to be low due to the limited amount of data available for thallium toxicity and the lack of any chronic or developmental toxicity studies.

Carcinogenesis: It is unknown whether thallium exposure may cause cancer. Studies on the cancer causing potential of this compound are needed. Limited studies in humans have not shown an increase in cancer mortality but these studies had methodological limitations that limit the conclusions that may be drawn from them (IRIS, 2000). Thallium exposure to isolated cells (both

mamallian and bacterial) did result in damage to DNA, suggesting that thallium is a genotoxicant (ATSDR, 1992). At this time USEPA believes there is insufficient evidence to decide on the carcinogenicity of thallium.

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Vanadium: CASRN 7440-62-2

Vanadium is a metallic element that is naturally present at low levels in the earth's crust. Vanadium is introduced into the environment by both natural processes or industrial activities such as steel production or combustion of coal or fuel oil (ATSDR, 1992). Vanadium is used in the manufacture of rubber, plastics, ceramics and other chemicals (ATSDR, 1992). Foodstuffs typically contain trace amounts of vanadium and the dietary intake of this mineral is about 0.01 to 0.02 mg per day. Vanadium has not been found to be an essential nutrient and does not appear to have a physiological role in the body. Exposure to vanadium may be assessed by measurement in several biological matrices, including blood and urine. Casarett and Doull indicate that municipal water supplies contain from about 1 to 6 ppb. The normal serum level for vanadium in humans is about 35 to 48 micrograms per 100 mL.

Vanadium has an affinity for fats and oils. After absorption, vanadium is primarily found in the fat. Bone and teeth stores also are important in making up the total body burden, and some amounts may also be found in kidney, liver and lung. Since vanadium is poorly absorbed, most of the ingested dose is eliminated in the feces over the course of several days. Exposure and human toxicity information for vanadium is largely based on inhalation and dust exposures in the workplace. Under such conditions the toxic action of vanadium is primarily on the respiratory tract, where it is an irritant. There are essentially no human data on the health effects of vanadium after exposure by ingestion. Data in animals are also limited but more extensive than

that for humans. In animal studies, exposure to vanadium has resulted in adverse effects in the kidney and spleen and during fetal development (ATSDR, 1992). The kidney and spleen effects were characterized as mild or minor in nature.

Non-Cancer Health Risks: HEAST lists an oral RfD for vanadium at 7E-3 mg/kg/day. The RfD is based on an oral dosing study conducted in rats using vanadium pentoxide (Stokinger et al., 1953). Decreased levels of cystine were observed in the hair of rats fed 179 parts per million vanadium pentoxide in their diet. Specific critical toxicologic endpoints were not identified. However, the no observed adverse effects level (NOAEL) in this study was reported as 17.9 ppm in the diet or 0.9 mg/kg/day. The NOAEL was divided by a factor of 10 to account for interspecies differences and 10 to protect sensitive subgroups in the exposed population. Confidence in the RfD is low due to the limited amount of toxicological data available for this compound. The Agency for Toxic Substances and Disease Registry (ATSDR) calculated an intermediate-duration minimal risk level (MRL) for vanadium based on a study by Domingo et al., (1985) that observed mild histological changes in the kidney, liver and spleen of rats orally dosed with sodium metavanadate. The NOAEL in this study was 0.3 mg vanadium/kg/day and the MRL was 3E-3 mg/kg/day. Note that the RfD was derived for vanadium pentoxide rather than vanadium itself. If based on the actual dose of vanadium in the Stokinger et al. study, the RfD would be approximately 5E-3 mg/kg/day and therefore very similar to the MRL.

Carcinogenesis: The USEPA has determined that there is insufficient evidence to classify vanadium as to carcinogenicity (IRIS, 2000). Oral dosing with vanadium did not produced tumors in one animal study (Schroeder and Balassa, 1967). However, this study was not sufficiently rigorous in its design to allow for a clear determination of carcinogenic potential (ATSDR, 1992).

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Zinc: CASRN 7440-66-6.

Zinc is a metallic element commonly found in soil and other environmental media. Zinc may enter environmental media either though natural process or human activity, such as coal burning, metal processing, steel production or waste combustion (ATSDR, 1994). Zinc compounds (primarily zinc oxide and zinc sulfide) are used in many applications including pigment manufacture, rubber production or wood preservation. Zinc compounds are also found in sun blocks, certain medical ointments and shampoos (ATSDR, 1994). Zinc is an essential dietary component and is present in small amounts in foods and vitamin supplements. The recommended daily allowances (RDA) for zinc, the amount that should be present in a healthy diet, are 5 mg/day for infants, 10 mg/day for children (1-10 yrs), 15 mg/day for men and 12 mg/day for women (NRC, 1989). This level of zinc is normally met by the typical daily food and water intake. Exposure to zinc may be assessed through blood measurements.

Zinc is readily absorbed in the body across the GI tract, although the degree of absorption may depend on the material with which it was ingested and the nutrient status of the individual. Persons with sufficient nutritional levels of zinc are reported to absorb 20 to 30% of ingested zinc (ATSDR, 1994). Once absorbed, zinc is distributed throughout the body with the majority stored in muscle tissue and bone (ATSDR, 1994). Excess zinc is eliminated rapidly from the body, with a half life reckoned in days (ATSDR, 1994).

While a limited zinc intake is required for good health, higher doses of zinc may result in toxicity. The primary symptoms of acute exposure to high doses of zinc involve the gastrointestinal system and include nausea and vomiting (ATSDR, 1994). Damage to the kidney, pancreas and circulatory system (i.e.,anemia) have also been reported in animals that have consumed high doses of zinc for extended periods of time. The doses associated with these effects are more than ten times the RDA. Exposure of laboratory animals to high concentrations of zinc (100 to 1000 times the RDA) has led to reproductive and developmental problems. These effects have not been observed in exposed human populations and it should be pointed out that insufficient intake of zinc may also lead to these types of problems.

Non-Cancer Health Risks: The oral RfD for zinc is 3E-1 mg/kg/day. The RfD is based on a human study that examined the effects of zinc dietary supplements on the nutritional status of copper and iron (Yadrick et al., 1989). High levels of zinc supplementation significantly

depressed levels of copper and iron associated proteins. More specifically, there was a 47 per cent decrease in erythrocyte superoxide dismutase (ESOD) concentrations in adult females after ten weeks of zinc exposure. The lowest observed adverse effects level (LOAEL) was 1 mg/kg/day. Because the data are derived from human populations, cross-species extrapolation was not required. The LOAEL was divided by a factor of 3 (to account for lack of a No Observed Adverse Effect Level but acknowledging zinc is a necessary nutrient), thus arriving at the RfD. Confidence in the RfD is medium, because the chosen study is consistent with a number of other human studies of zinc toxicity. Confidence is only medium because the human studies only involved short-term (rather than lifetime) dosing.

Carcinogenesis: The US EPA has determined that there is insufficient evidence to classify zinc as to carcinogenicity (IRIS, 2000). Zinc has not been found to cause cancer in humans and no sufficiently clear evidence of cancer in experimental animals has been obtained.

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